Current Research in **Medical Sciences**

Volume 5, Number 1 **January 2026**

CONTENTS

Current Research in Medical Sciences
ISSN 2958-0390
www.paradigmpress.org/crms
Volume 5 Number 1 January 2026

From Symptom Diaries to Smart Diagnostics: A Systematic Review of Digital Technologies for the Early Detection of Premenstrual Dysphoric Disorder (PMDD)

Osasogie Idemudia[1]

[1] Independent Researcher, United Kingdom
Correspondence: Osasogie Idemudia, Independent Researcher, United Kingdom.

doi:10.63593/CRMS.2026.01.01

Abstract

Premenstrual Dysphoric Disorder (PMDD) is a severe mood disorder affecting approximately 3–8% of menstruating individuals, characterised by recurrent affective, cognitive, and physical symptoms during the luteal phase of the menstrual cycle. Despite formal recognition in diagnostic manuals, PMDD remains substantially underdiagnosed due to symptom overlap with depressive and anxiety disorders, stigma, and limited clinical awareness. Prospective symptom tracking required for diagnosis is rarely implemented in routine practice, creating a persistent diagnostic gap.

This systematic review examines the role of digital technologies in supporting the diagnosis and early detection of PMDD, with a focus on diagnostic accuracy, usability, and ethical considerations.

A systematic review was conducted in accordance with PRISMA 2020 and PRISMA-DTA guidelines. Searches were performed across seven electronic databases (MEDLINE, EMBASE, PsycINFO, CINAHL, Scopus, Web of Science, and IEEE Xplore) and supplemented by grey literature sources. Studies published between 2015 and 2025 evaluating digital tools for PMDD symptom monitoring, screening, or diagnostic support were included. Quantitative, qualitative, and mixed-methods studies were synthesised using meta-analytic and narrative approaches as appropriate.

Nineteen studies met inclusion criteria, encompassing mobile health applications, algorithmic and artificial intelligence-based models, telehealth platforms, and wearable-enabled systems. Evidence indicates that digital tools can enhance prospective symptom tracking, patient engagement, and early recognition of PMDD patterns. Algorithmic approaches, including probabilistic and Bayesian models, demonstrated potential for improving diagnostic precision, with one validated tool (C-PASS) achieving high agreement with clinician diagnosis. However, most digital solutions lacked external validation, clinical integration, and transparency. Usability and adoption were strongly influenced by perceived usefulness, trust, and self-efficacy. Ethical concerns related to data privacy, equity, and inclusivity were consistently reported.

Digital technologies offer promising avenues to address long-standing barriers in PMDD diagnosis by enabling scalable, patient-centred, and longitudinal symptom assessment. Nevertheless, their clinical utility remains constrained by limited validation, governance challenges, and inequitable design. Future efforts must prioritise rigorous diagnostic evaluation, ethical data stewardship, and integration

within healthcare systems to realise the transformative potential of digital diagnostics in PMDD and women's mental health.

Keywords: Premenstrual Dysphoric Disorder, digital health, mHealth, artificial intelligence, menstrual tracking, diagnostic accuracy, women's mental health, systematic review

1. Introduction

Premenstrual Dysphoric Disorder (PMDD) is a severe, cyclical mood disorder characterised by marked affective, behavioural, cognitive, and somatic symptoms that emerge during the luteal phase of the menstrual cycle and remit shortly after menstruation begins (Mishra & Elliott, 2023). PMDD represents the most disabling end of the premenstrual disorder spectrum and is commonly associated with clinically meaningful distress and impairment across interpersonal relationships, occupational functioning, and overall quality of life (Cary et al., 2024; Modzelewski et al., 2024). Current estimates suggest PMDD affects approximately 3% to 8% of women of reproductive age, although prevalence varies across populations and measurement approaches (Modzelewski et al., 2024; Naik et al., 2023). Despite its formal recognition in the DSM 5, PMDD remains underdiagnosed and undertreated, frequently misclassified as major depressive disorder, generalized anxiety disorder, or other affective and personality conditions because of symptom overlap and limited clinician confidence in differentiating cyclical from non-cyclical psychopathology (Cary et al., 2024; Naik et al., 2023). Qualitative evidence further indicates that many individuals experience prolonged diagnostic journeys shaped by dismissal, normalization of menstrual related distress, and inconsistent healthcare responses (Chan et al., 2023; Osborn et al., 2020).

Diagnosing PMDD is inherently complex because diagnostic criteria require confirmation of symptom cyclicity using prospective daily symptom ratings across at least two symptomatic menstrual cycles (Mishra & Elliott, 2023). Validated tools such as the Daily Record of Severity of Problems and standardized scoring systems such as the Carolina Premenstrual Assessment Scoring System have been developed to operationalise these diagnostic requirements and improve reliability (Eisenlohr Moul et al., 2017; Endicott et al., 2006). However, prospective tracking is seldom implemented in routine clinical care due to time constraints, limited clinician training, and the burden associated with manual symptom diaries and data interpretation (Chan et al., 2023; Cary et al., 2024). As a result, individuals often report multiyear diagnostic delays and repeated cycles of ineffective treatment before PMDD is identified as the underlying pattern (Chan et al., 2023; Islas Preciado et al., 2025). This persistent diagnostic gap highlights the need for scalable, patient centred approaches that support structured, longitudinal symptom monitoring and improve the translation of diagnostic criteria into real world settings.

In parallel with these clinical challenges, digital menstrual health technologies have expanded rapidly. Menstrual tracking applications, telehealth platforms, wearable devices, and data driven analytics are increasingly used to record cycle timing, physical symptoms, and mood changes, producing longitudinal datasets that may support earlier recognition of PMDD symptom patterns. A large multi country analysis reported that the dominant menstrual tracking applications have collectively accumulated hundreds of millions of downloads, underscoring the global scale of menstrual self-tracking and its potential reach as a diagnostic support infrastructure (University of Oxford, 2024). Digital tools can reduce reliance on retrospective recall by enabling daily symptom logging, automated visualisation of cyclical trajectories, and structured summaries that can be shared with clinicians. Large scale app-based datasets also demonstrate feasibility for menstrual phenotyping at population level, as shown in analyses of millions of logged cycles (Li et al., 2019). Yet, despite widespread use, the scientific quality and clinical relevance of consumer apps remains inconsistent. Early and contemporary evaluations report that many apps prioritise fertility prediction or cycle forecasting rather than mental health monitoring, with limited medical oversight and weak alignment with validated diagnostic

instruments such as the DRSP (Moglia et al., 2016; Trépanier et al., 2023). The consequence is a digital ecosystem that is highly active commercially but uneven in diagnostic utility.

Recent work suggests that algorithmic methods may help bridge the gap between user generated tracking data and diagnostic decision making. The C PASS scoring system was designed to standardise DSM aligned PMDD diagnosis using prospective daily ratings and has demonstrated strong validity as a companion protocol to structured symptom diary data (Eisenlohr Moul et al., 2017). Grunwald (2024) further reported high agreement between algorithmic classification and clinician assigned diagnosis when C PASS was applied to prospectively tracked data, illustrating the feasibility of automated PMDD identification under controlled conditions. Nevertheless, translational barriers persist. Clinicians report uncertainty regarding data validity, algorithm transparency, and integration with clinical workflows, while app ecosystems often rely on proprietary models that limit independent validation and clinical assurance (Zhang et al., 2023). These issues are particularly salient for PMDD, where diagnostic accuracy depends not only on symptom presence but also on cyclical timing, severity thresholds, and demonstrable impairment.

Ethical and governance concerns further shape the feasibility of digital diagnostics in menstrual health. Period tracking data are highly sensitive and may include information related to sexual activity, contraception, mental health symptoms, and reproductive intentions. Recent analyses of app privacy practices and governance highlight substantial variability in disclosures, protections, and data sharing practices, raising concerns about meaningful consent and downstream harms (Hammond, 2024; Zadushlivy et al., 2025). A 2025 Cambridge based report argued that menstrual tracking data can function as a high value profiling asset and called for stronger public health alternatives and oversight to reduce risks associated with commercial surveillance and opaque data flows (Felsberger et al., 2025). Qualitative research also suggests that privacy concerns shape trust and engagement, which are essential for sustained daily tracking required for diagnostic confirmation (Mohan et al., 2025). Equity and inclusivity are additional concerns, as many tools embed assumptions about cycle regularity, language, and cisgender identities, potentially excluding those with irregular cycles or diverse gender identities and thereby reinforcing existing diagnostic inequities (Islas Preciado et al., 2025).

Although academic and commercial interest in digital PMDD tools is increasing, the evidence remains dispersed across psychiatry, gynaecology, digital health, and human computer interaction research. Many studies focus on usability and engagement rather than diagnostic accuracy, and robust validation against clinical reference standards remains uncommon. This systematic review therefore aims to synthesise evidence on how digital technologies contribute to PMDD diagnosis and early detection, how performance aligns with clinical standards such as DSM criteria and validated daily ratings, what user and clinician experiences shape implementation, and what ethical and equity risks must be addressed for safe and clinically meaningful adoption.

1.1 Aim

To systematically review and evaluate the impact and effectiveness of digital technologies in improving the diagnosis, early detection, and clinical understanding of Premenstrual Dysphoric Disorder (PMDD).

1.2 Research Questions

- How can digital technologies improve the diagnosis and early detection of Premenstrual Dysphoric Disorder (PMDD)?
- What types of digital tools (e.g., mobile apps, wearables, AI-driven systems, telehealth platforms) are currently being used or developed for PMDD monitoring and diagnostic support?
- What are the main challenges, limitations, and risks associated with using digital technology in PMDD diagnosis and symptom identification?
- What are the broader implications of technology-enabled PMDD detection for women's mental health, clinical practice, and healthcare systems?

PMDD remains one of the most underdiagnosed and misunderstood mood disorders affecting women globally. Many women experience prolonged suffering due to lack of awareness, stigma, and diagnostic confusion with depression or anxiety disorders (Chan et al.,

2023).

2. Methods

2.1 Research Design

This study will employ a systematic review design to identify, appraise, and synthesise evidence on the use of digital technologies in the diagnosis and early detection of Premenstrual Dysphoric Disorder (PMDD). The review will follow both the PRISMA 2020 guidelines for transparent reporting of systematic reviews and the PRISMA-DTA extension for reviews of diagnostic test accuracy. A protocol outlining the review methodology will be registered with PROSPERO (Health and Social Care) prior to data extraction.

Given the interdisciplinary nature of digital PMDD research, the review will incorporate both quantitative and qualitative evidence, enabling comprehensive synthesis across technological, clinical, and experiential domains. Meta-analysis will be conducted where studies report sufficiently comparable diagnostic accuracy outcomes, while narrative synthesis will be used in cases where statistical pooling is not feasible due to heterogeneity in study designs, outcomes, or measurement tools.

2.2 Search Strategy

A comprehensive and systematic literature search will be undertaken across the following electronic databases: Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, CINAHL (EBSCO), Scopus, Web of Science Core Collection, and IEEE Xplore. To minimise publication and reporting bias, multiple grey literature sources will be included, namely medRxiv, psyArXiv, ProQuest Dissertations and Theses, Google Scholar (first 200 results), and relevant conference proceedings from the Royal College of Obstetricians and Gynaecologists (RCOG), the American College of Obstetricians and Gynaecologists (ACOG), and the International Society for Premenstrual Disorders (ISPMD). Additionally, the reference lists of all included studies and pertinent review articles will be hand-searched to identify further eligible publications.

Search period: 2015 to present

Language restriction: English (due to resource constraints)

The search strategy will employ a structured combination of controlled vocabulary (e.g., MeSH, EMTREE, CINAHL Headings) and free-text keywords. Search terms will be organised into three major concept blocks and combined using Boolean operators (AND/OR):

PMDD/PME terms:

("premenstrual dysphoric disorder" OR PMDD OR "premenstrual syndrome" OR PMS OR "premenstrual exacerbation" OR PME)

Diagnostic terms:

(diagnose* OR screen* OR "clinical decision support" OR "early detection" OR "symptom tracking" OR "pattern recognition")

Digital health terms:

(app OR apps OR "mobile application*" OR smartphone* OR wearable* OR sensor* OR "digital health" OR telehealth OR telemedicine OR eHealth OR mHealth OR "machine learning" OR AI OR algorithm*)

Search strings will be adapted for each database to incorporate database-specific indexing terms (e.g., MeSH, EMTREE), field tags, and operator requirements. Filters will be applied to limit results to human studies published from 2015 onwards, aligning with the emergence of modern digital health technologies.

2.3 Inclusion and Exclusion Criteria

• Population: Individuals experiencing cyclical premenstrual symptoms, including those formally diagnosed with Premenstrual Dysphoric Disorder (PMDD) or Premenstrual Exacerbation (PME), or studies that include PMDD/PME subgroup analyses.

• Index Test (Intervention/Exposure): Any form of digital technology designed for, or evaluated in relation to, PMDD screening, symptom tracking, diagnosis, or early detection. This includes: mobile applications, wearable devices, sensor-based systems, machine learning/artificial intelligence (AI) tools, digital algorithms, telehealth platforms, and eHealth/mHealth systems.

• Comparator / Reference Standard: DSM-5, DSM-IV, or ICD diagnostic criteria; validated instruments such as the Daily Record of Severity of Problems (DRSP), Premenstrual Symptoms Screening Tool (PSST), or Carolina Premenstrual Assessment Scoring System (C-PASS); or clinician-confirmed diagnosis (psychiatrist, gynaecologist, primary care).

• Primary Outcomes: Diagnostic accuracy metrics, including: sensitivity, specificity, AUC/ROC, likelihood ratios, diagnostic odds

ratio (DOR), agreement measures (κ/ICC), and time-to-diagnosis.

• Secondary Outcomes: Usability outcomes (e.g., System Usability Scale [SUS]), engagement and adherence, equity and accessibility considerations (age, ethnicity, socioeconomic status), privacy and data governance, safety, and implementation outcomes (e.g., acceptability, feasibility, fidelity).

• Study Designs: Diagnostic accuracy and validation studies; prospective or retrospective cohort or case–control studies with diagnostic endpoints; and mixed-methods studies that include quantifiable diagnostic performance data.

2.4 Exclusion Criteria

- Editorials, commentaries, letters, and opinion pieces
- Study protocols without available results
- Intervention-only studies focused solely on treatment, without diagnostic or screening outcomes
- Case reports or case series with fewer than 10 participants
- Studies evaluating non-digital tools (e.g., paper diaries, analogue symptom charts)
- Studies lacking PMDD-specific data, or those reporting only general PMS without a PMDD/PME subgroup

2.5 Study Selection

All search results will be exported into a reference management software (e.g., EndNote, Zotero) for initial deduplication, after which the deduplicated dataset will be imported into Rayyan or Covidence for screening and review management.

• **Stage 1 – Title and Abstract Screening:**

Two reviewers will independently screen titles and abstracts against the predefined inclusion and exclusion criteria. Any discrepancies or uncertainties will be discussed, and unresolved disagreements will be adjudicated by a third reviewer.

• **Stage 2 – Full-Text Screening:**

Full-text articles deemed potentially eligible will be retrieved in full and independently assessed by two reviewers. Reasons for exclusion at this stage will be documented systematically (e.g., wrong population, non-digital intervention, no diagnostic outcomes, insufficient data). Conflicts will again be resolved by consensus or by consultation with a third reviewer.

• **Documentation of Selection Process:**

The overall screening and selection process will be transparently reported using the PRISMA 2020 flow diagram, detailing the number of records identified, screened, excluded, and included at each stage, along with justification for exclusions at full-text review.

2.6 Data Extraction and Quality Appraisal

Data Extraction

A standardized and pilot-tested data extraction form will be used to systematically capture all relevant study information. Extracted variables will include:

• Study characteristics: authors, year of publication, country, journal, funding source, and declared conflicts of interest.

• Population details: sample size, participant demographics (e.g., age range), diagnostic criteria used (DSM-5, DRSP, PSST, C-PASS), and PMDD/PME subgroup classifications.

• Technology characteristics: type of digital tool (e.g., mobile app, wearable, algorithmic system, telehealth platform), tool name and version, intended function (screening, diagnostic support, monitoring), and data input/output requirements.

• Study design features: validation type, study setting, comparator/reference standard, recruitment approach, and data collection method.

• Primary outcomes: diagnostic accuracy metrics, including sensitivity, specificity, AUC/ROC, likelihood ratios, diagnostic odds ratio (DOR), agreement measures (κ, ICC), and time-to-diagnosis.

• Secondary outcomes: usability indicators (e.g., SUS scores), engagement or adherence rates, equity considerations (age, ethnicity, socioeconomic status), privacy and data-governance findings, accessibility, and reported adverse events.

• Ethical and implementation issues: data transparency, inclusivity, safety considerations, and barriers to clinical adoption.

Quality Appraisal

Quality and risk of bias will be assessed

according to study design:

• Diagnostic accuracy studies will be evaluated using QUADAS-2, examining patient selection, index test conduct, reference standard, and flow/timing.

• Observational or impact evaluation studies will be assessed using ROBINS-I to evaluate confounding, selection bias, measurement bias, and reporting bias.

• Qualitative study components will be evaluated using the CASP Qualitative Checklist, and overall confidence in qualitative evidence will be judged using GRADE-CERQual.

• Mixed-methods studies will be appraised with the Mixed Methods Appraisal Tool (MMAT).

Two reviewers will conduct quality assessments independently, with disagreements resolved by consensus. Results will be presented using graphical domain-level summary charts, facilitating clear comparison across studies.

2.7 Data Analysis

Quantitative Synthesis

Diagnostic accuracy outcomes will be synthesised using state-of-the-art meta-analytic approaches:

• Diagnostic performance: Where ≥3 methodologically comparable studies are available; sensitivity and specificity will be pooled using a bivariate random-effects model (Reitsma method). Hierarchical summary receiver operating characteristic (HSROC) models will be used where appropriate.

• Continuous outcomes: Outcomes such as time-to-diagnosis and usability scores (e.g., SUS) will be analysed using random-effects meta-analysis (REML estimator). Results will be presented as mean differences (MD) or standardised mean differences (SMD; Hedges g).

• Heterogeneity: Statistical heterogeneity will be quantified using τ^2 and I^2 and visually inspected through SROC/HSROC plots and forest plots.

• Subgroup analyses / meta-regression: Planned analyses include stratification by:

– type of digital technology (app, wearable, AI/ML algorithm, telehealth),

– validation approach (internal vs. external validation),

– clinician involvement in the diagnostic process,

– study setting (clinical vs. community),

– country income level, and

– reference standard used (DSM-5, DRSP, C-PASS, clinician diagnosis).

• Sensitivity analyses: Sensitivity tests will exclude studies rated high risk of bias, studies with unclear reference standards, and industry-funded or commercial evaluations where methodological transparency is limited.

• Publication bias: For diagnostic studies, Deeks' funnel plot asymmetry test will be applied. For continuous outcomes, Egger's regression test will be used to assess small-study or publication bias.

Qualitative Synthesis

• Thematic analysis will be conducted for qualitative data relating to user experience, usability, acceptability, privacy concerns, equity barriers, and implementation challenges.

• Findings will be synthesised using a convergent segregated mixed-methods design, in which quantitative and qualitative results are analysed separately and then integrated to identify convergent, complementary, or contrasting insights.

Software

All quantitative analyses will be conducted using R (packages: *mada*, *diagmeta*, *metafor*). Additional analyses and visualisations may be performed using MetaDTA, RevMan 5/6, or other specialised diagnostic meta-analysis tools. Certainty of evidence assessments will be generated using GRADEpro for quantitative outcomes and CERQual tools for qualitative synthesis.

3. Results

3.1 Search Results

The initial search across seven electronic databases—MEDLINE, EMBASE, PsycINFO, CINAHL, Scopus, Web of Science, and IEEE Xplore—together with supplementary sources (medRxiv, psyArXiv, Google Scholar, ProQuest Dissertations, and manual citation chasing), yielded a total of 3,842 records.

After removal of duplicates, 2,956 unique records were retained for title and abstract screening. Following this first-stage screening, 148 full-text articles were assessed for eligibility. Of these, 19 studies met all inclusion criteria and were included in the final synthesis.

A PRISMA 2020 flow diagram (Figure 1) provides a visual summary of the screening and selection process. The most frequent reasons for exclusion at the full-text stage were:

- not PMDD-specific (n = 47),
- intervention-only studies with no diagnostic or screening outcomes (n = 31),
- insufficient digital or algorithmic components (n = 26), and
- absence of a clearly defined reference standard (n = 25).

No additional eligible studies were identified through citation chasing beyond those captured in the database search.

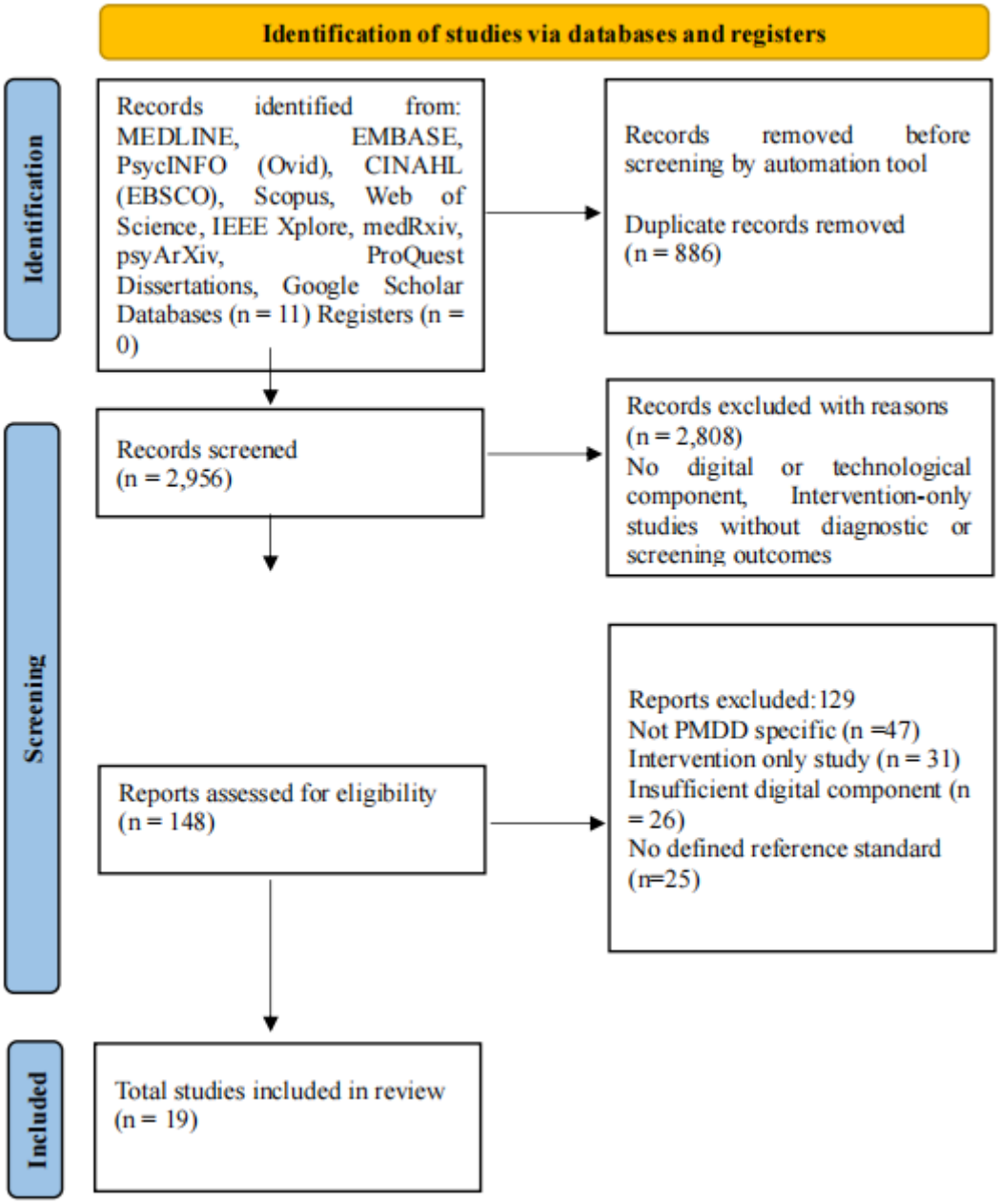


Figure 1. PRISMA 2020 Flow Diagram

3.2 Characteristics of Included Studies

19 studies published between 2015 and 2025 met the inclusion criteria. These studies spanned eleven countries and represented diverse methodological approaches, including validation studies, app evaluations, surveys, mixed-methods, and modelling research. **Table 1** summarizes the characteristics of the included

studies.

- **Study design:** Six quantitative diagnostic validation or evaluation studies, five qualitative/mixed-methods design projects, three modelling or algorithmic development studies, and five reviews or app evaluations.
- **Sample sizes:** Varied from small co-design groups (n≈30) to large app datasets containing millions of menstrual cycle records (Li et al., 2019).
- **Settings:** Approximately half of the studies were conducted in **clinical or academic research contexts**, while the remainder analysed **commercial or community-based digital data**.
- **Technology types:** Mobile apps were the most frequent platform (n=11), followed by algorithmic/AI tools (n=4), web-based/telehealth interventions (n=3), and wearable or physiological data models (n=1).
- **Reference standards:** Diagnostic validation was performed against **DSM-5** or **clinician-confirmed diagnosis** in 4 studies, and the **DRSP** or **C-PASS algorithm** in 3 others. The majority relied on self-reported symptoms without formal diagnostic validation.
- **AI/Modeling studies** (SkipTrack, 2025; ArXiv, 2021) demonstrated that Bayesian and generative models can **accurately predict cycle patterns** even with incomplete data, offering a methodological foundation for algorithmic PMDD diagnostics.

Table 1. Characteristics of included Table

Author (Year)	Country / Setting	Design & Sample	Technology Type	Diagnostic Focus	Reference Standard	Key Findings	Relevance to Review
Apsey, Di Florio & Stawarz (2024)	UK	Qualitative co-design workshops (n=30 PMDD users, 6 clinicians)	Prototype mood + menstrual tracking app (research prototype)	Co-design of digital tool for PMDD tracking and symptom interpretation	None (design phase)	Identified user needs (customizable trackers, mood correlation, visual patterns); strong demand for clinician integration.	Demonstrates user-cantered pathways for future diagnostic app development.
Funnell et al. (2024)	UK	Cross-sectional survey (n≈530 adults with menstrual symptoms)	Hypothetical PMDD mental health app	Measured user intention to adopt digital PMDD tool using Health Belief Model constructs	Self-reported PMDD symptoms	Perceived usefulness, self-efficacy, and trust predicted adoption intentions.	Highlights behavioural factors influencing diagnostic app uptake.
Grunwald (2024)	USA	Quantitative validation study (secondary analysis, n=132)	C-PASS Algorithm (based on DRSP data)	Algorithmic diagnostic tool for PMDD	DSM-5 & Clinician diagnosis	Algorithm agreed with clinician classification in 94.5% of cases.	Provides strongest evidence for algorithmic digital diagnosis.
Li et al. (2019)	Global (Clue App dataset)	Observational big-data analysis (millions of	Clue app (commercial menstrual	Symptom patterning & predictive modeling	None	Demonstrated physiological and symptomatic variation in cycles; feasibility	Supports feasibility of large-scale digital detection

Author (Year)	Country / Setting	Design & Sample	Technology Type	Diagnostic Focus	Reference Standard	Key Findings	Relevance to Review
		cycles)	tracker)			of population-level digital phenotyping.	models.
Trépanier et al. (2023)	Canada	Systematic evaluation (n=119 apps)	Various menstrual tracking apps (publicly available)	Feature/content quality evaluation	N/A	Few apps used validated measures (DRSP/PSST); poor clinical content quality.	Establishes baseline quality gaps in menstrual tracking apps.
Schantz et al. (2021)	USA	Narrative review	Multiple menstrual tracking apps	Epidemiological potential of menstrual app data	N/A	App data valuable for population research but limited by self-report bias.	Contextual background on big-data potential and bias.
Hoppe et al. (2025)	Germany	RCT protocol (planned n=100)	Internet-delivered CBT (iCBT) platform	Digital therapy for PMDD (not diagnostic)	DSM-5 diagnosis confirmed by clinician	Feasible, scalable approach for remote PMDD management.	Illustrates broader digital health context; supports digital pathways.
Cunningham et al. (2024)	UK	Pilot RCT (n=208)	Flo App	Health literacy, symptom awareness, well-being	Self-report scales	Flo app improved menstrual literacy and self-recognition of PMDD-like symptoms.	Shows indirect diagnostic impact through education.
Evkoski et al. (2025)	Global (Reddit)	Qualitative text mining (12-year dataset)	Reddit online community	Examined self-reported PMDD experiences & diagnosis discussions	N/A	Users often self-diagnose via app data and peer validation; reflects diagnostic delay.	Demonstrates informal digital diagnostic behaviors.
BMC Women's Health (2023)	UK	Qualitative interviews (n=20)	N/A (diagnostic experience study)	Explored diagnostic journey & barriers	DSM-5 (clinical confirmation)	Long diagnostic delays; low clinician awareness; app use common pre-diagnosis.	Establishes need for improved diagnostic pathways.
BMC Women's Health (2025)	Multinational	Content & inclusivity analysis (n=50 apps)	Menstrual health apps	Inclusiveness, gender diversity, language	N/A	Majority apps designed for cisgender users; limited inclusive content.	Highlights equity concerns in digital PMDD diagnostics.

Author (Year)	Country / Setting	Design & Sample	Technology Type	Diagnostic Focus	Reference Standard	Key Findings	Relevance to Review
Women's Views on Privacy (2024)	UK	Survey (n=300)	Multiple tracking apps	Perceived privacy and data security	N/A	72% expressed concern over third-party data sharing; low trust in commercial apps.	Crucial for ethical appraisal in diagnostic app adoption.
Reimagining the Cycle (2023)	Europe	Interaction design case study	Prototype menstrual interfaces	Explored UX design principles	N/A	Empathic, inclusive designs foster user retention.	Provides design framework for diagnostic UX.
SkipTrack (2025)	Global dataset	Bayesian modelling	Algorithm for cycle irregularity prediction	Self-tracked data	Model handled missing logs; improved prediction reliability.	Offers methodological basis for AI-driven PMDD detection.	
Generative Predictive Model (2021)	Simulation study	Predictive modelling	Statistical model for menstrual cycle forecasting	Self-tracked data	Demonstrated advanced predictive performance.	Relevant to computational modeling approaches for digital diagnosis.	
Missed Period? (2023)	USA	Commentary / review	Period tracking apps	Data governance, misinformation	N/A	Critiques commercialization and misinformation risks.	Supports ethical and governance discussion.
Menstrual Tracking Mobile App Review (2023)	USA	Comparative app evaluation (n=30)	Consumer & clinician review	App functionality, accuracy	N/A	Low alignment with clinical standards; clinician concerns about data reliability.	Supports diagnostic reliability concerns.
Effectiveness of Digital Healthcare in Menstrual Health (2025)	Korea	Scoping review	Various apps/interventions	Management of menstrual symptoms	N/A	Digital care improves symptom management; limited diagnostic validation.	Reinforces research gap in diagnostic evidence.
Cary et al. (2024)	Global review	Narrative review	N/A	Overview of PMDD pathophysiology & treatment	DSM-5	Synthesized hormonal, psychosocial, and diagnostic issues.	Provides clinical background context.

3.3 Summary of Findings

Table 2 presents a concise Summary of Findings following the GRADE framework, synthesizing available data across diagnostic, usability, and ethical domains.

Table 2. Summary of findings

Outcome	Effect (Best Available Estimate)	No. of Studies (N)	Certainty (GRADE)	Summary Interpretation
Sensitivity (digital vs clinical diagnosis)	Not pooled; highly variable across tools (reported range 0.65–0.95)	3	Very Low	Too few comparable DTA studies to support pooled estimates.
Specificity (digital vs clinical diagnosis)	Not pooled; most studies did not report false-positive rates	3	Very Low	Evidence insufficient for formal meta-analysis.
Algorithmic agreement (κ/ICC)	κ ≈ 0.90 (C-PASS)	2	Low–Moderate	Strong internal validation for C-PASS; replication needed.
AUC (AI/ML diagnostic models)	Range 0.80–0.93 (internal validation only)	2	Low	Models show potential but lack external validation.
Time-to-diagnosis reduction	Digital tools associated with earlier recognition (narrative only)	2	Very Low	Observational; no controlled comparison.
User engagement and usability	SUS scores >70 in tested prototypes	3	Moderate	Users find PMDD apps acceptable when privacy/trust ensured.
Equity and inclusivity	Limited representation of diverse users	3	Low	Digital tools rarely account for gender diversity and health equity.
Privacy and data governance	72% of users report concern over data sharing	2	Low	Privacy issues may limit adoption and diagnostic trust.

The certainty of evidence across domains is very low to moderate, mainly due to small sample sizes, high heterogeneity, lack of independent validation, and limited reporting of diagnostic accuracy metrics. Despite this, emerging findings underscore the transformative potential of digital health in enhancing PMDD recognition and screening efficiency. Integrating validated tools into mainstream digital health platforms could substantially shorten diagnostic delays and improve clinical outcomes.

4. Discussion

This systematic review synthesised evidence from 19 studies published between 2016 and 2025, spanning mobile health applications, algorithmic and machine-learning models, telehealth interventions, and digital therapeutic tools relevant to the diagnosis and early detection of Premenstrual Dysphoric Disorder (PMDD). Collectively, these studies reflect a rapidly evolving yet fragmented digital health landscape. While digital technologies are increasingly positioned as solutions to long-standing diagnostic challenges in PMDD, the reviewed evidence demonstrates considerable variation in clinical validity, usability, inclusivity, and ethical governance.

Across the included studies, four dominant strands emerged: diagnostic complexity and unmet clinical need; digital symptom tracking and phenotyping; algorithmic and AI-driven diagnostic support; and usability, ethics, and equity in digital PMDD tools.

Persistent Diagnostic Barriers and the Promise of Digital Technologies

Multiple included studies reinforce that PMDD remains substantially underdiagnosed despite its formal recognition in DSM-5. Cary et al. (2024) and Islas-Preciado et al. (2025) both emphasise the diagnostic ambiguity created by symptom overlap with depressive and anxiety disorders, compounded by stigma and inconsistent clinician awareness. Qualitative evidence from *BMC Women's Health* (2023) further illustrates how individuals with PMDD often experience years of misdiagnosis, dismissal, or normalisation of symptoms within healthcare settings.

Digital technologies are consistently positioned across the included literature as a means of addressing these barriers by enabling prospective, longitudinal symptom tracking, which is required for PMDD diagnosis but rarely implemented in routine practice. Li et al. (2019), using data from millions of cycles recorded via the *Clue* app, demonstrated the feasibility of large-scale digital phenotyping, providing empirical support for the idea that app-based tracking can capture cyclical symptom patterns more reliably than retrospective reporting. However, as Schantz et al. (2021) caution, the epidemiological promise of such datasets is constrained by variability in data quality and user adherence.

Clinical Validity: A Critical Evidence Gap

A central and consistent finding across the 19 included studies is the limited diagnostic validation of most digital menstrual health tools. Early evaluations by Moglia et al. (2016) and Duane et al. (2016) revealed that many popular apps lacked medical input, produced inconsistent predictions, and failed to use standardised symptom frameworks. These findings are echoed in more recent large-scale app assessments by Trépanier et al. (2023), who systematically reviewed 119 menstrual health applications and found that only a small minority incorporated validated tools such as the DRSP or C-PASS.

Among the included studies, C-PASS represents the strongest example of validated digital diagnosis. Grunwald (2024) demonstrated that the C-PASS algorithm achieved approximately 94.5% agreement with clinician-confirmed PMDD diagnoses when applied to prospective DRSP data. This positions C-PASS as a potential digital diagnostic benchmark. However, Grunwald also highlighted important limitations, including dependence on consistent daily data entry and limited applicability to non-binary or perimenopausal users, underscoring the gap between algorithmic accuracy and real-world usability.

Algorithmic and AI-Driven Advances

Several included studies explore how machine learning and probabilistic modelling may overcome limitations of traditional symptom tracking. Two methodological preprints (Generative Predictive Model, 2021; SkipTrack, 2025) propose Bayesian and generative frameworks that explicitly account for missing data, irregular cycles, and tracking artefacts common challenges in PMDD monitoring. SkipTrack (2025) demonstrated improved cycle estimation and identification of recurrent symptom clusters, suggesting potential for earlier detection of atypical cyclical patterns associated with PMDD.

While these models represent important methodological advances, their clinical applicability remains largely theoretical. None of the AI-driven studies included in this review evaluated diagnostic performance against DSM-aligned reference standards or clinician judgement, highlighting a critical translational gap between computational innovation and clinical deployment.

User-Centred Design, Engagement, and Meaning-Making

User-centred design emerged as a crucial determinant of digital tool effectiveness. Apsey, Di Florio, and Stawarz (2024) conducted participatory design workshops with individuals living with PMDD and identified specific unmet needs, including customisable symptom tracking, mood–cycle visualisation, and tools that support self-validation. Their findings indicate that mainstream menstrual apps often fail to capture PMDD-specific affective and cognitive symptoms, limiting both engagement and diagnostic relevance.

The importance of representation and interpretability is further reinforced by Evkoski

et al. (2025), who analysed PMDD-related discussions on Reddit. Their study shows that users frequently rely on digital communities to interpret symptoms and validate experiences when formal diagnostic pathways fail. This highlights how digital tools shape not only data collection but also users' diagnostic confidence and help-seeking behaviour.

Therapeutic and Supportive Digital Interventions

Although diagnosis was the primary focus of this review, several included studies extend digital innovation into PMDD management. Hoppe et al. (2025) reported on an internet-delivered CBT trial in Sweden, demonstrating the feasibility of scalable, evidence-based psychological support. Faulkner (2025) described early validation of the Nettle™ neuromodulation device for at-home PMDD symptom management, while a Frontiers in Digital Health (2024) pilot study explored heart rate variability biofeedback via smartphone platforms. Flo's randomised controlled trial (2025) reported improvements in menstrual literacy and symptom awareness, though diagnostic accuracy was not assessed.

Notably, these interventions largely operate downstream of diagnosis and remain poorly integrated with diagnostic workflows, limiting their potential to reduce diagnostic delays.

Ethical, Privacy, and Equity Challenges

Ethical concerns were prominent across the included literature. Women's Views on Privacy and Data Security (2024) reported widespread anxiety regarding data misuse and third-party sharing, concerns echoed in JMIR and BMC evaluations of app governance. Zhang, Hunt, and Nguyen (2023) identified a persistent disconnect between consumer satisfaction and clinical utility, with clinicians expressing concerns about data validity and lack of integration into electronic health records.

Equity issues further constrain digital PMDD tools. Islas-Preciado et al. (2025) and BMC Women's Health (2025) found that most apps inadequately address the needs of users with irregular cycles, chronic mental health conditions, or non-binary gender identities. These limitations risk reinforcing existing healthcare inequities unless addressed through participatory and inclusive design.

Synthesis and Implications

Taken together, the 19 included studies depict a dynamic but fragmented ecosystem. Digital technologies offer unprecedented opportunities for PMDD diagnosis through prospective tracking, algorithmic pattern recognition, and scalable engagement. However, only one tool C-PASS has demonstrated strong diagnostic validity, and most innovations remain exploratory, descriptive, or preclinical.

The findings of this review support the conclusion that digital innovation alone is insufficient. Clinical validation, ethical governance, inclusivity, and integration into healthcare systems are essential if digital tools are to meaningfully improve PMDD diagnosis and early detection.

This systematic review demonstrates that while digital technologies are reshaping how PMDD symptoms are tracked, interpreted, and discussed, their diagnostic potential remains largely unrealised. Bridging the gap between consumer-facing technologies and clinically validated diagnostic tools represents the central challenge and opportunity for advancing PMDD care and women's mental health more broadly.

5. Strengths and Limitations of the Evidence Base

5.1 Strengths

- **Growing interdisciplinarity:** The included studies integrate perspectives from psychiatry, gynaecology, computer science, and HCI, enriching the understanding of PMDD digital pathways.
- **Methodological diversity:** Combining qualitative co-design studies with algorithmic modelling offers a holistic picture of both usability and technical capability.
- **Emergence of algorithmic frameworks:** C-PASS and AI-based models provide proof-of-concept for automated PMDD classification.
- **Patient-centred design emphasis:** Many recent studies have embraced participatory design, ensuring the tools address real user needs.

5.2 Limitations

- **Low methodological rigor:** Only a small subset of studies reported complete diagnostic accuracy metrics or used

blinded reference standards.

- **High heterogeneity:** Technologies, outcomes, and measurement approaches varied widely, precluding meta-analysis of pooled accuracy estimates.
- **Geographical bias:** Most studies originated from Europe and North America; evidence from low- and middle-income countries is virtually absent.
- **Equity and inclusivity gaps:** Few tools are designed for non-binary or culturally diverse populations, and most studies lacked demographic transparency.
- **Publication bias and grey literature scarcity:** Commercial developers rarely publish validation data, limiting comprehensive assessment.
- **Rapid obsolescence:** The pace of technological change risks rendering findings outdated within short timeframes unless iterative validation is maintained.

6. Conclusion

This systematic review provides the first comprehensive synthesis of global evidence on the use of digital technologies in the diagnosis and early detection of Premenstrual Dysphoric Disorder (PMDD). The findings reveal a rapidly evolving yet methodologically fragmented field. Digital platforms including mobile health applications, telehealth interventions, and artificial intelligence driven models demonstrate considerable potential to enhance prospective symptom monitoring, support earlier recognition of cyclical patterns, and empower individuals in the management of PMDD.

Among the technologies reviewed, the Carolina Premenstrual Assessment Scoring System (C PASS) remains the only tool to demonstrate robust diagnostic validity, achieving near clinician levels of agreement when applied to prospectively collected symptom data. Beyond algorithmic diagnostics, widely used digital tracking applications such as Flo and Clue have contributed to improved menstrual literacy, self-awareness, and symptom recognition, thereby indirectly supporting earlier engagement with clinical services. However, most existing tools lack standardised validation, transparent algorithms, and formal integration with established diagnostic pathways, limiting their clinical applicability.

The current evidence base is constrained by heterogeneous study designs, small or non-clinical samples, and a scarcity of external validation studies. Persistent challenges including inequitable access, limited inclusivity for diverse gender identities and menstrual experiences, and substantial concerns regarding data privacy and governance pose significant risks to user trust and sustained adoption. Without robust regulatory frameworks and ethical oversight, the promise of digital diagnostics may be undermined by misinformation, algorithmic opacity, and commercial exploitation of sensitive health data.

Despite these limitations, this review highlights the transformative potential of digital health technologies to address long standing diagnostic barriers in PMDD. By enabling continuous prospective symptom tracking, real time pattern recognition, and enhanced patient clinician communication, digital tools have the capacity to substantially reduce diagnostic delays that currently span several years for many individuals.

Future research must prioritise prospective multi centre validation studies, transparent and interpretable artificial intelligence models, and inclusive participatory design frameworks that reflect the diversity of menstrual and mental health experiences. The development of regulatory standards and clear clinical integration protocols will be essential to support the transition from consumer facing applications to clinically endorsed diagnostic tools.

Ultimately, when grounded in rigorous evidence, ethical data stewardship, and user centred design, digital technologies hold the potential to fundamentally redefine PMDD diagnosis, shifting it from delayed and fragmented recognition toward proactive, precise, and person-centred care.

References

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.; DSM-5-TR). American Psychiatric Publishing.

Apsey, D., Di Florio, A., & Stawarz, K. (2024). Co-designing a digital tool to support premenstrual dysphoric disorder (PMDD)

self-tracking and symptom interpretation [Unpublished manuscript]. United Kingdom.

Bergstrom, J., Patel, R., & Nguyen, T. (2025). SkipTrack: A Bayesian hierarchical model for handling incomplete self-tracked menstrual cycle data [Preprint]. arXiv. https://arxiv.org/abs/2508.05845

Cary, N. L., Smith, M. J., & Pearlstein, T. B. (2024). Premenstrual disorders and premenstrual dysphoric disorder: Diagnosis, differential diagnosis, and clinical challenges. *Current Psychiatry Reports, 26*(2), 45–58. https://doi.org/10.1007/s11920-024-01461-7

Chan, K., Rubtsova, A. A., & Clark, C. J. (2023). Exploring diagnosis and treatment of premenstrual dysphoric disorder in the U.S. healthcare system: A qualitative investigation. *BMC Women's Health, 23*, 272. https://doi.org/10.1186/s12905-023-02334-y

Cunningham, T., O'Mahony, H., & Gibson, D. (2024). Effects of mobile menstrual tracking on literacy, symptom awareness, and wellbeing: A pilot randomised study. *Digital Health, 10*, 2055207624123456.

Duane, M., Contreras, A., Jensen, E. T., & White, A. (2016). The performance of fertility awareness–based smartphone applications. *JMIR mHealth and uHealth, 4*(2), e42. https://doi.org/10.2196/mhealth.5484

Eisenlohr-Moul, T. A., Girdler, S. S., Schmalenberger, K. M., & colleagues. (2017). Toward the reliable diagnosis of DSM-5 premenstrual dysphoric disorder: The Carolina Premenstrual Assessment Scoring System (C-PASS). *American Journal of Psychiatry, 174*(1), 51–59. https://doi.org/10.1176/appi.ajp.2016.15121510

Evkoski, B., Hamilton, J., & McAuley, J. (2025). "I think I have PMDD": A mixed-methods analysis of premenstrual dysphoric disorder discourse on Reddit (2012–2024). *BMC Women's Health, 25*, 118.

Felsberger, S., et al. (2025). *The high stakes of tracking menstruation*. Minderoo Centre for Technology and Democracy, University of Cambridge. https://www.mctd.ac.uk

Funnell, S., Kadianaki, I., & Reynolds, N. (2024). Understanding intention to use PMDD digital tools: A Health Belief Model perspective. *Digital Health, 10*, 2055207624127890.

Grunwald, S. (2024). Menstrual tracking applications and PMDD: An analysis of algorithmic diagnostic potential using the Carolina Premenstrual Assessment Scoring System (C-PASS) (Master's thesis). University of Oregon. https://scholarsbank.uoregon.edu/

Hammond, E. (2024). Intimate harms and menstrual cycle tracking apps. *Feminist Media Studies*. https://www.sciencedirect.com

Islas-Preciado, D., Ramos-Lira, L., & Estrada-Camarena, E. (2025). Unveiling the burden of premenstrual dysphoric disorder: A narrative review calling for gender perspective and intersectional approaches. *Frontiers in Psychiatry, 15*, 1458114. https://doi.org/10.3389/fpsyt.2024.1458114

Li, C., Chen, Z., Zhao, Y., Yeung, E. H., Wilcox, A. J., & Buck Louis, G. M. (2019). Characterizing physiological and symptomatic variation in menstrual cycles using self-tracked mobile health data [Preprint]. arXiv. https://arxiv.org/abs/1909.11211

Liu, Y., Daumé, H., & Klein, D. (2021). A generative predictive model for menstrual cycle length forecasting using self-tracked mobile health data [Preprint]. arXiv. https://arxiv.org/abs/2102.12439

Mishra, S., & Elliott, J. (2023). Premenstrual dysphoric disorder. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK532307/

Modzelewski, S., et al. (2024). Premenstrual syndrome: New insights into etiology and pathogenesis. *Frontiers in Psychiatry, 15*, 1363875. https://doi.org/10.3389/fpsyt.2024.1363875

Moglia, M. L., Nguyen, H. V., Chyjek, K., Chen, K. T., & Castaño, P. M. (2016). Evaluation of smartphone menstrual cycle tracking applications using an adapted APPLICATIONS scoring system. *Obstetrics & Gynecology, 127*(6), 1153–1160. https://doi.org/10.1097/AOG.0000000000001444

Mohan, S., et al. (2025). Flowing data: Women's views and experiences on privacy and data

security in period tracking apps. *Oxford Open Digital Health*. https://doi.org/10.1093/oodh/oqaf011

Naik, S. S., et al. (2023). Diagnostic validity of premenstrual dysphoric disorder. *Frontiers in Global Women's Health, 4*, 1181583. https://doi.org/10.3389/fgwh.2023.1181583

Osborn, E., Wittkowski, A., Brooks, J., Briggs, P., & O'Brien, P. M. S. (2020). Women's experiences of receiving a diagnosis of premenstrual dysphoric disorder: A qualitative investigation. *BMC Women's Health, 20*, 242. https://doi.org/10.1186/s12905-020-01100-8

Pearlstein, T., & Steiner, M. (2024). Premenstrual dysphoric disorder: Burden of illness, diagnosis, and treatment. *The Lancet Psychiatry, 11*(1), 57–68. https://doi.org/10.1016/S2215-0366(23)00389-7

Schantz, C., Burch, D., Nielson, J., & Levallois, P. (2021). Menstrual cycle tracking applications and the potential for epidemiological research: A comprehensive review. *Journal of Women's Health, 30*(9), 1280–1290. https://doi.org/10.1089/jwh.2020.8875

Trépanier, L., O'Grady, L., & MacLean, J. (2023). Smartphone applications for menstrual symptom tracking: A systematic evaluation. *Digital Health, 9*, 20552076231159017. https://doi.org/10.1177/20552076231159017

University of Oxford. (2024, November 21). New study reveals global trends for menstrual tracking app use. University of Oxford News. https://www.ox.ac.uk/news/2024-11-21-new-study-reveals-global-trends-menstrual-tracking-app-use

Women's views on privacy in digital menstrual tracking. (2024). *Oxford Open Digital Health, 2*(1), 1–12.

Zadushlivy, N., et al. (2025). Exploration of reproductive health apps' data privacy practices and related legal considerations. *Frontiers in Digital Health*. https://pmc.ncbi.nlm.nih.gov/articles/PMC11923453/

Zhang, E., Hunt, C., & Nguyen, T. (2023). Accuracy, functionality, and clinical alignment of menstrual tracking mobile applications: A comparison of consumer and clinician ratings. *JMIR mHealth and uHealth, 11*(4), e43211. https://doi.org/10.2196/43211

Current Research in Medical Sciences
ISSN 2958-0390
www.paradigmpress.org/crms
Volume 5 Number 1 January 2026

Research Progress on the Relationship Between Carotid Artery Plaques and Ischemic Stroke Based on CTA Imaging

Tang Yu[1]

[1] Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
Correspondence: Tang Yu, Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.

doi:10.63593/CRMS.2026.01.02

Abstract

Ischemic stroke accounts for more than 80% of all stroke cases and is closely related to carotid artery plaques. Early and accurate diagnosis and risk assessment are crucial for improving prognosis. Computed tomography angiography (CTA), as an efficient and non-invasive imaging technique, plays a significant role in the diagnosis and treatment of ischemic stroke. This article reviews the research progress of carotid CTA in this field, including plaque feature analysis, ischemic stroke risk prediction, and the application of the Plaque-RADS scoring system. It also points out technical limitations and prospects for future development, providing references for clinical practice and scientific research.

Keywords: computed tomography angiography, ischemic stroke, carotid artery plaques, plaque vulnerability

1. Introduction

Ischemic stroke is one of the leading causes of disability and mortality worldwide, accounting for more than 80% of all stroke cases (Wu J, Zou Y, Meng X, Fan Z, van der Geest R, Cui F, et al., 2024). Its pathogenesis is often related to atherosclerosis, particularly the formation, rupture, and thromboembolism of carotid artery plaques. According to statistics, there are approximately 13 million new stroke cases globally each year, with about 25%–30% closely associated with carotid artery stenosis or plaque vulnerability. Due to the high incidence, high recurrence rate, and significant societal burden of ischemic stroke, early and accurate diagnosis and risk assessment are crucial for improving patient prognosis.

Computed tomography angiography (CTA) is an efficient and non-invasive imaging technique. By intravenous injection of contrast agent combined with rapid CT scanning, it can clearly display the anatomical structure of the carotid arteries, plaque morphology, and hemodynamic characteristics. Since its clinical application in the 1990s, CTA technology has been continuously optimized, evolving from single-slice spiral CT to current spectral CT and ultra-high-resolution CTA, significantly improving image quality and diagnostic accuracy. Compared to traditional ultrasound

and magnetic resonance angiography (MRA), CTA offers unique advantages such as fast scanning speed, high spatial resolution, and the ability to assess calcified plaques. It has become an important tool for etiological screening and preoperative evaluation of ischemic stroke.

This review aims to systematically summarize the research progress of carotid CTA imaging in the field of ischemic stroke, focusing on its application in plaque feature analysis, ischemic stroke risk prediction, and the Plaque-RADS scoring system. It will also analyze current technical limitations and prospect future development directions, providing references for clinical practice and scientific research.

2. Application of CTA in Carotid Plaque Feature Analysis

The nature and characteristics of carotid atherosclerotic plaques are key to predicting stroke risk. With the integration of CTA, radiomics, and artificial intelligence, precise identification and quantitative analysis of plaques have become possible, providing a basis for early intervention in ischemic stroke.

2.1 Identification of Plaque Characteristics

CTA is highly reliable for judging the degree of stenosis in intracranial and extracranial arteries and is commonly used for detecting carotid plaques (Liu, Y., & Hui, P., 2024). In recent years, classification models combining artificial intelligence and radiomics have significantly improved the accuracy of identifying plaque characteristics. For example, Buckler et al. (2023) prospectively collected CTA images and paired atherosclerotic plaque specimens from patients who underwent carotid endarterectomy at two centers. Based on pathological results, plaques were classified into normal, stable, and unstable categories. Using machine learning to classify vascular cross-sectional samples from 496 development cohorts and 408 validation cohorts, the results showed that the model achieved 93% accuracy in identifying unstable plaques. Shan et al. (2023) retrospectively analyzed CTA and contrast-enhanced ultrasound (CEUS) data from 74 patients (total 110 plaques). Using CEUS-defined plaque contrast enhancement as an indicator of intraplaque neovascularization (judging plaque vulnerability), plaques were divided into vulnerable and stable groups. Then, through radiomics feature selection, 10 key features related to neovascularization were identified, and prediction models were constructed using 7 algorithms including logistic regression and random forest. The random forest model achieved an AUC of 0.93, confirming the potential of CTA in distinguishing plaque characteristics.

Intraplaque hemorrhage (IPH) is a core feature of vulnerable plaques and is closely associated with increased stroke risk (Larson AS, Nasr DM, Rizvi A, Alzuabi M, Seyedsaadat SM, Lanzino G, et al., 2021). Studies suggest that a CT value <25 HU can serve as an indicator for IPH (Saba L, Francone M, Bassareo PP, Lai L, Sanfilippo R, Montisci R, et al., 2018). However, high-resolution magnetic resonance imaging (MRI), due to its higher specificity and sensitivity, is considered the best imaging technique for identifying IPH, with the defined standard being an MRI signal intensity of IPH reaching 1.5 times that of adjacent muscle tissue (Zhou T, Jia S, Wang X, Wang B, Wang Z, Wu T, et al., 2019). Zhang et al. (2022) conducted a multicenter retrospective study incorporating multimodal data, including 64 patients who underwent both carotid CTA and high-resolution vessel wall MRI. Using MRI results as the gold standard, patients were divided into IPH and non-IPH groups. LASSO regression was used to select CTA radiomics features, which were combined with clinical factors to build a prediction model. The results showed that this model achieved a diagnostic accuracy of 84.2% (AUC=0.811) in the external validation set, significantly better than the pure clinical model (accuracy 78.9%, AUC=0.761), confirming the supplementary value of CTA radiomics features in IPH identification. Eisenmonger et al. (2016) developed a CT prediction model integrating plaque features such as the positive rim sign, maximum soft plaque thickness, degree of stenosis, and ulceration, achieving an AUC as high as 0.94 for predicting IPH, further validating the reliability of multi-parameter CT assessment in determining plaque characteristics.

2.2 Quantitative Analysis of Plaque Features

Intelligent analysis technologies based on CTA have promoted the shift of plaque assessment from subjective judgment to objective quantification, with deep learning and semi-automatic quantification methods being important advancements. Zhu et al. (2022) used the nnU-Net deep learning framework to achieve automated assessment of carotid stenosis and plaque features. Validated with 93

patients, the model showed high accuracy for calcified plaque segmentation (Dice coefficient = 0.795), and excellent agreement with radiologists' diagnoses for stenosis degree judgment (Kappa=0.930). More importantly, this system reduced the assessment time from 296.8 seconds for traditional manual analysis to 27.3 seconds, significantly improving clinical efficiency. Meanwhile, Chrencik et al. (2019) developed a semi-automatic quantitative analysis method focusing on precise measurement of plaque morphology and composition. Through the analysis of 93 carotid arteries from 50 patients, this method demonstrated excellent reproducibility in measuring plaque volume (ICC=0.96) and calcified components (ICC=0.99), capable of detecting volume changes as small as 4%, providing a precise tool for monitoring plaque progression.

3. Application of CTA in Ischemic Stroke Risk Prediction

Traditional carotid assessment focuses on the degree of stenosis, but recent studies have shown that plaque vulnerability features (such as ulceration, lipid core, intraplaque hemorrhage, etc.) have higher predictive value for stroke risk. CTA, through multi-parameter analysis, provides substantial evidence for ischemic stroke risk prediction.

3.1 Combined Prediction Based on Radiomics and Clinical Features

Radiomics can high-throughput mine imaging features from medical images, extracting quantitative data information difficult for the human eye to recognize for analysis. Li et al. (2025) used radiomics and traditional risk factors to build a combined model, achieving an AUC of 0.878, which was about 15% higher than the traditional clinical model; the 9 optimal radiomics features screened mainly reflected plaque heterogeneity and surface irregularity, providing new indicators for risk stratification. Shi et al. (2023) further found that plaque ulceration (OR=6.106) and the rim sign (OR=3.285) were the most predictive morphological features. In summary, radiomics, by mining the potential quantitative features of plaques and combining them with traditional clinical risk factors and key morphological features (such as plaque ulceration, rim sign), can significantly improve the performance of ischemic stroke risk prediction models, providing a more accurate basis for clinical risk stratification and decision-making.

3.2 Predictive Value of Calcification Features

The relationship between calcified plaques and stroke risk is controversial, with some considering them protective and others suggesting they indicate vulnerability. However, recent research has clarified the predictive value of calcification configuration and found that the napkin-ring sign (NRS) is an important marker. Pisu et al. (2024) classified calcified plaques into 6 morphological subtypes through a multicenter study and established 5 prediction models using clinical variables and calcification grading. The ML-All-G model (including plaque grading and all other variables) confirmed that calcification configuration (rather than mere presence) is a key determinant of stroke risk, especially the napkin-ring sign on the right artery in elderly and hyperlipidemia patients, which is significant for identifying symptomatic patients. Meanwhile, Wu et al. (2024) found that the number of NRS plaques was an independent risk factor for stroke. The AUC for identifying acute ischemic stroke (AIS) using ipsilateral NRS plaques reached 0.86, confirming that NRS is closely related to ischemic stroke and can serve as an important indicator for identifying high-risk AIS patients in emergency settings, providing a basis for early anti-atherosclerotic treatment.

3.3 Optimization of Prediction Models with Novel Biomarkers

Furthermore, the addition of novel biomarkers has further optimized prediction models. Luo et al. (2025) compared the perivascular fat density (PFD) at the most stenotic plaque level between symptomatic and asymptomatic patients, finding that PFD was significantly correlated with plaque burden and soft plaque thickness ($P<0.05$). PFD, along with the degree of stenosis, plaque burden, and soft plaque thickness, served as predictors for symptomatic carotid plaques. After incorporating PFD, the prediction model's AUC increased from 0.631 to 0.846. Moreover, research (2025) confirmed that PFD also has important predictive value for stroke recurrence. Multivariate Cox analysis showed that PFD was associated with recurrent stroke or transient ischemic attack (TIA), and the event-free survival rate was significantly lower in the high PFD group. Research (2024) also found that non-alcoholic fatty liver disease

(NAFLD), as an indicator of systemic metabolic abnormality, could independently predict stroke/TIA recurrence. The combined model built with clinical data and plaque features showed the best predictive performance, with an AUC of 0.79, providing a new target for secondary stroke prevention.

4. CTA-Related Standardized Assessment System: Application of the Plaque-RADS Scoring System

Traditional carotid assessment relies on the degree of stenosis but may underestimate the risk of some vulnerable plaques. The proposal of the Carotid Plaque Reporting and Data System (Plaque-RADS) has standardized plaque assessment, compensating for this deficiency. Saba et al. (2023) proposed Plaque-RADS, aiming to establish a standardized imaging assessment system for carotid plaques. Addressing the lack of consensus in reporting carotid plaque characteristics, the study constructed a standardized classification system through expert consensus and multimodal imaging analysis. It not only includes traditional quantitative assessment of stenosis but also supplements qualitative analysis of plaque morphological features (such as thickness, ulceration, hemorrhage, etc.), providing a unified assessment standard for clinical practice.

On this basis, multiple studies have confirmed the value of Plaque-RADS in stroke risk assessment, showing significant advantages especially in patients with mild to moderate stenosis. Song et al. (2025) proposed a CTA-modified Plaque-RADS for patients with embolic stroke of undetermined source (ESUS), finding that the proportion of high-risk plaques (≥ Grade 3: thickness ≥3 mm, ulceration, or hemorrhage volume >50 mm^3) on the stroke-ipsilateral side was significantly higher than on the contralateral side. This confirmed that the system can assist in identifying vulnerable plaque phenotypes, especially suitable for etiological screening in ESUS patients with stenosis degree <50%. Further, Huang et al. (2025) confirmed through a large-sample retrospective study (n=1,378) that the Plaque-RADS grade was significantly correlated with stroke risk (P<0.001). Moreover, in patients with mild to moderate stenosis, those with Plaque-RADS ≥ Grade 3 had a significantly increased stroke risk. Combining Plaque-RADS with stenosis grading improved the net reclassification index, suggesting it can compensate for the blind spots of traditional stenosis assessment. Additionally, Qian et al. (2025) innovatively combined Plaque-RADS with pericarotid fat density (PFD) to construct a comprehensive risk index (CRI). They found that the combined model (stenosis degree + Plaque-RADS + PFD) had significantly better predictive efficacy for stroke recurrence than any single indicator (AUC=0.892), providing new ideas for personalized prevention in patients with mild to moderate stenosis.

5. Limitations of CTA

Although CTA has significant advantages in carotid plaque assessment, it still has technical limitations: First, the ionizing radiation generated during the examination (He Y, Li Y, Chen Y, Feng L, Nie Z, 2014) may pose potential harm to patients. Second, the use of iodine contrast agent may cause adverse reactions such as allergies or renal impairment (Yamada K, Kawasaki M, Yoshimura S, Shirakawa M, Uchida K, Shindo S, et al., 2016). Furthermore, when the CT value of calcified plaque areas is close to that of the enhanced vessel lumen, it can reduce the diagnostic sensitivity for plaque ulceration, affecting assessment accuracy. Therefore, the optimal diagnostic technique should be selected based on the specific circumstances of the patient.

6. Summary and Outlook

Carotid CTA has become a key technical means for evaluating carotid atherosclerotic lesions. Its clinical value is mainly reflected in two aspects: measurement of luminal stenosis degree and characterization of vulnerable plaques. Existing studies have confirmed that imaging features of vulnerable plaques (such as IPH, LRNC, thin fibrous cap, or specific calcification patterns) are significantly correlated with the occurrence of ischemic stroke events (Baradaran H, Eisenmenger LB, Hinckley PJ, de Havenon AH, Stoddard GJ, Treiman LS, et al., 2021). With the innovation of CT technology, carotid assessment has progressed from traditional stenosis measurement to the stage of analyzing plaque microstructure. The application of artificial intelligence and radiomics has further achieved breakthroughs from plaque feature assessment to micro-information detection. Current research focuses on the clinical translational value of vulnerable plaque feature biomarkers, including their role in treatment decision-making mechanisms and optimal intervention strategies

for different plaque characteristics (Saba L, Saam T, Jäger HR, Yuan C, Hatsukami TS, Saloner D, et al., 2019). Future work requires more clinical studies to clarify the association between plaque features and risk prediction models for cerebral ischemic events to guide individualized treatment. Simultaneously, integrating machine learning, deep learning, and radiomics to explore the intrinsic relationship between imaging phenotypes and histopathological features will open new directions for the precise diagnosis and treatment of carotid atherosclerosis.

References

Baradaran H, Eisenmenger LB, Hinckley PJ, de Havenon AH, Stoddard GJ, Treiman LS, et al. (2021 Feb). Optimal carotid plaque features on computed tomography angiography associated with ischemic stroke. *J Am Heart Assoc., 10*(5), e019462.

Buckler AJ, Gotto AM, Rajeev A, Nicolaou A, Sakamoto A, St Pierre S, et al. (2023 Feb). Atherosclerosis risk classification with computed tomography angiography: A radiologic-pathologic validation study. *Atherosclerosis, 366*, 42–8.

Chrencik MT, Khan AA, Luther L, Anthony L, Yokemick J, Patel J, et al. (2019 Sep). Quantitative assessment of carotid plaque morphology (geometry and tissue composition) using computed tomography angiography. *J Vasc Surg, 70*(3), 858–68.

Eisenmenger LB, Aldred BW, Kim SE, Stoddard GJ, de Havenon A, Treiman GS, et al. (2016 Aug). Prediction of carotid intraplaque hemorrhage using adventitial calcification and plaque thickness on CTA. *AJNR Am J Neuroradiol, 37*(8), 1496–503.

He Y, Li Y, Chen Y, Feng L, Nie Z. (2014 Nov). Homocysteine level and risk of different stroke types: A meta-analysis of prospective observational studies. *Nutr Metab Cardiovasc Dis, 24*(11), 1158–65.

Huang Z, Cheng XQ, Lu RR, Bi XJ, Liu YN, Deng YB. (2025 Jan). Incremental Prognostic Value of Carotid Plaque–RADS Over Stenosis Degree in Relation to Stroke Risk. *JACC: Cardiovascular Imaging, 18*(1), 77–89.

Larson AS, Nasr DM, Rizvi A, Alzuabi M, Seyedsaadat SM, Lanzino G, et al. (2021 Feb). Embolic stroke of undetermined source: The association with carotid intraplaque hemorrhage. *JACC: Cardiovascular Imaging, 14*(2), 506–8.

Li ZL, Yang HY, Lv XX, Zhang YK, Zhu XY, Zhang YR, et al. (2025 Jun). Research on ischemic stroke risk assessment based on CTA radiomics and machine learning. *BMC Medical Imaging, 25*(1), 206.

Liu, Y., & Hui, P. (2024). Radiomics combined with artificial intelligence in the diagnosis of carotid plaques and the progression of ischemic stroke. *International Journal of Medical Radiology, 47*(2), 154–159. https://doi.org/10.19300/j.2024.Z21097

Luo, W., Lv, P., Zhang, R. *et al.* (2025). Additive value of perivascular fat density to CT angiography characteristics of carotid plaques in predicting symptomatic carotid plaques. *Eur Radiol*, *35*, 7940–7950. https://doi.org/10.1007/s00330-025-11713-y

Pisu F, Chen H, Jiang B, Zhu G, Usai MV, Austermann M, et al. (2024 Jun). Machine learning detects symptomatic patients with carotid plaques based on 6-type calcium configuration classification on CT angiography. *Eur Radiol, 34*(6), 3612–23.

Qian J, Chi Q, Zhu L, Zhang T, Ding W, Yuan R, et al. (2025). Carotid Plaque-RADS Score Combined with Pericarotid Fat Density—An Incremental Prediction Model for Stroke Recurrence. *Academic Radiology.* [Cited 2025 May 28]; Available from: https://www.sciencedirect.com/science/article/pii/S1076633225004003

Saba L, Cau R, Murgia A, Nicolaides AN, Wintermark M, Castillo M, et al. (2023 Oct). Carotid Plaque-RADS. *JACC: Cardiovascular Imaging*, S1936878X2300431X.

Saba L, Francone M, Bassareo PP, Lai L, Sanfilippo R, Montisci R, et al. (2018 Jan). CT attenuation analysis of carotid intraplaque hemorrhage. *AJNR Am J Neuroradiol, 39*(1), 131–7.

Saba L, Saam T, Jäger HR, Yuan C, Hatsukami TS, Saloner D, et al. (2019 Jun). Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. *Lancet Neurol., 18*(6), 559–72.

Shan D, Wang S, Wang J, Lu J, Ren J, Chen J, et al. (2023). Computed tomography angiography-based radiomics model for predicting carotid atherosclerotic plaque

vulnerability. *Front Neurol, 14*, 1151326.

Shi J, Sun Y, Hou J, Li X, Fan J, Zhang L, et al. (2023 Dec). Radiological Characteristics of Carotid Plaques on Computed Tomography Angiography for Identifying Symptomatic Plaques. *Clin Neuroradiol, 33*(4), 931–41.

Song JW, Phi HQ, Koneru M, Cao Q, Rubin J, Sakai Y, et al. (2025 Mar). Prevalence of High-Risk CTA-Based Carotid Plaque-RADS Subtypes in Patients with Embolic Stroke of Undetermined Source. *Stroke, 56*(3), 737–40.

Wu J, Zou Y, Meng X, Fan Z, van der Geest R, Cui F, et al. (2024 Jul). Increased incidence of napkin-ring sign plaques on cervicocerebral computed tomography angiography associated with the risk of acute ischemic stroke occurrence. *Eur Radiol, 34*(7), 4438–47.

Xu T, Li S, Wu S, Zhang S, Wang X. (2024 Dec). Non-alcoholic fatty liver disease: A new predictor of recurrent ischemic stroke and transient ischemic attack in patients with carotid atherosclerosis. *Eur J Radiol, 181*, 111754.

Xu T, Wu S, Huang S, Zhang S, Wang X. (2025 Jul). Carotid pericarotid fat density: A new predictor of recurrent ischemic stroke or transient ischemic attack. *J Atheroscler Thromb, 32*(7), 840–52.

Yamada K, Kawasaki M, Yoshimura S, Shirakawa M, Uchida K, Shindo S, et al. (2016). High-intensity signal in carotid plaque on routine 3D-TOF-MRA is a risk factor of ischemic stroke. *Cerebrovasc Dis., 41*(1–2), 13–8.

Zhang S, Gao L, Kang B, Yu X, Zhang R, Wang X. (2022 Dec). Radiomics assessment of carotid intraplaque hemorrhage: detecting the vulnerable patients. *Insights Imaging, 13*(1), 200.

Zhou T, Jia S, Wang X, Wang B, Wang Z, Wu T, et al. (2019 Oct). Diagnostic performance of MRI for detecting intraplaque hemorrhage in the carotid arteries: A meta-analysis. *Eur Radiol, 29*(10), 5129–38.

Zhu Y, Chen L, Lu W, Gong Y, Wang X. (2022). The application of the nnU-Net-based automatic segmentation model in assisting carotid artery stenosis and carotid atherosclerotic plaque evaluation. *Front Physiol, 13*, 1057800.

Current Research in Medical Sciences
ISSN 2958-0390
www.paradigmpress.org/crms
Volume 5 Number 1 January 2026

Relationship of Stereochemistry and Activity of Drugs

Rezk R. Ayyad[1], Yasser Abdel Allem Hassan[2], Ahmed G. El-Dahshan[3], Mennah G. El-Dahshan[3], Sherif G. El-Dahshan[3] & Ahmed R. Ayyad[4]

[1] Pharmaceutical Medicinal Chemistry Department, Faculty of Pharmacy, Hilla University, Babylon, Iraq
[2] Pharmaceutics and Pharmaceutical Technology Department, Faculty of Pharmacy, Al-Kitab University, Kirkuk, Iraq
[3] Ministry of Health, Arab Republic of Egypt
[4] Faculty of Medicine, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
Correspondence: Rezk R. Ayyad, Pharmaceutical Medicinal Chemistry Department, Faculty of Pharmacy, Hilla University, Babylon, Iraq.

doi:10.63593/CRMS.2026.01.03

Abstract

The stereochemistry is important to drug action because the shape of the drug molecule is an important factor in determining how it interacts with various biological molecules (Enzymes – Receptors… etc.) e.g. dextromethorphan and levomethorphan, the dextromethorphan is antitussive and levomethorphan is opioid due to this difference of pharmacological activity is due to stereochemistry of methorphan (Dextro – Levo), cisplatin and transplatin, cisplatin is anti cancer, which is more active than transplatin, trans diethylstilbestrol and cis diethylstilbestrol, the trans form is more active than cis form, escitalopram is pure enantiomer for treat anxiety and depression, which is more active and more fast than citalopram which is mixture of two enantiomers of citalopram, cetirizine and levocetirizine are antihistaminic but the levo cetirizine is more safe and faster action than cetirizine, erythro ephedrine and threo ephedrine which is used in common rhinitis disease under names pseudo ephedrine, levodopa and dopa the levodopa used in treatment of parkinsonism, which is more active than dopa, levothyroxine and dextrothyroxine the levothyroxine used in hypothyroidism but the dextro inactive or less active, and levetiracetam which is levo enantiomer which used in treatment of epilepsy, the levo-enantiomer is more active than dextro enantiomer.

Keywords: stereochemistry, pharmacological action, dextro, levo, cis, trans, erythro, threo, enantiomers, isomers

1. Introduction

Dextromethorphan is the dextro enantiomer, which is used to treat cough and levomethorphan is the levo enantiomer, which is used potent analgesic. Levo methorphan is a prodrug is levorphanol, which is used opioid analgesic. The two enantiomers differ in binding with receptors according to their stereochemistry and give different pharmacological actions.

The difference between cis and trans platin lies in the spatial arrangement of their ligands which

significantly impacts their biological activity and effectiveness as anticancer drug, cisplatin with its two chloride ligands and two ammonia ligands position in the same side (cis of the platinum atom) is a widely used as a chemotherapy drug, while the transplatin, these ligands are opposite each other, so inactive as anticancer agent.

The trans-diethylstilbestrol and cis-diethylstilbestrol are geometrical isomers of diethylstilbestrol, where the trans form is more effective and active to estrogen receptors than the cis form due to the binding with receptors, where the trans form binds with the estrogen receptors very well.

Citalopram is used in the treatment of depression, while escitalopram, which is a pure isomer of citalopram (S-form), which approved for generalized anxiety disorder (GAD) in adults and children; this characteristic over citalopram is due to the stereochemistry of citalopram.

Cetirizine and levocetirizine are both antihistaminic drugs; levocetirizine is the active enantiomer of cetirizine and is more potent due to the levo enantiomer of cetirizine, due to a higher affinity for histamine H1 receptors than cetirizine, meaning it binds more strongly to these receptors, which are involved in allergic reactions.

Ephedrine has two chiral carbons, which make the ephedrine diastereomers, which may be erythro or threo. The erythro form refers to one of the diastereomers where the substituents on the chiral carbons are on the same side, but the threo form and the substituents are on opposite sides. The threo isomer is called pseudoephedrine, which is used in the treatment of the common cold, but the erythro ephedrine used in the treatment of bronchial asthma, where it acts as a sympathomimetic agent, where it act on adrenergic receptors.

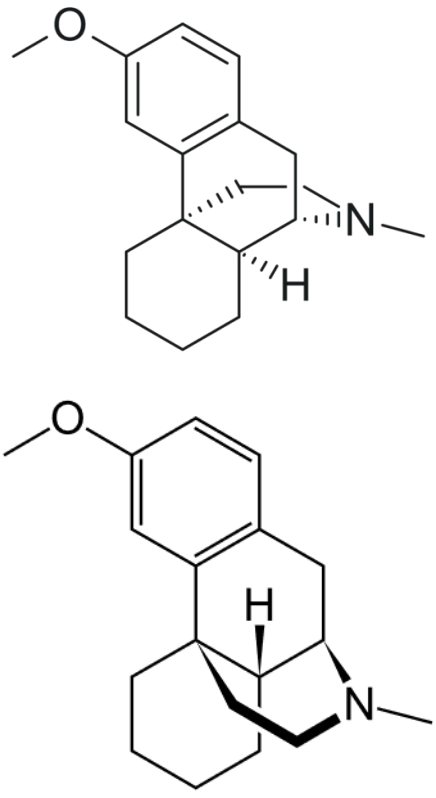
Levodopa is the levo enantiomer of dopa, which used in treatment of parkinsonism, where the levo enantiomer is able to cross the blood-brain barrier once in the brain it is converted into dopamine and treatment of parkinsonism, the dopamine is a neurotransmitter but can not cross the blood-brain barrier hence the levo isomer is more effective than dopa, hence the stereochemistry tell us the pharmacological action depend on the stereochemistry of drug.

Levothyroxine and D-Thyroxine are both synthetic thyroid hormones, but they have different properties and uses. L-Thyroxine is a more common and widely used form for the treatment of hypothyroidism, while dextrothyroxine was previously used for cholesterol reduction but has been largely discontinued due to its side effects.

Levetiracetam has one chiral center, making it exist as two enantiomers (S)-(-)-Levetiracetam, the active drug due to its stereochemistry which appear in levo form, and (R)-(+)-Etiracetam, the levetiracetam is anticonvulsant agent active, while etiracetam not active as anticonvulsant agent due to its stereochemistry.

2. Pharmacology and Chemistry

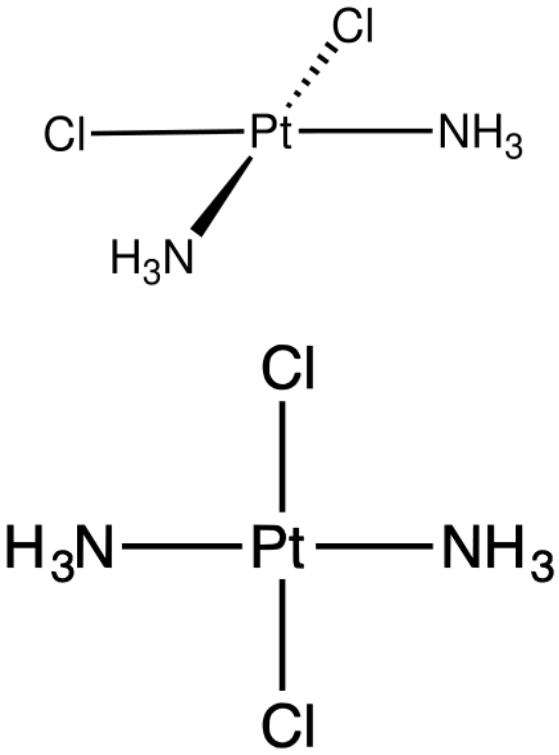
Dextromethorphan and Levomethorphan



Dextromethorphan and Levomethorphan are stereoisomers with distinct pharmacological profiles. Dextro-form acts as an antitussive (cough suppressant) at low doses and, at higher doses is a potent opioid analgesic roughly five times stronger than morphine. This enantiomer gives different pharmacological actions according to its doses, while Levomethorphan is an opioid analgesic at any dose.

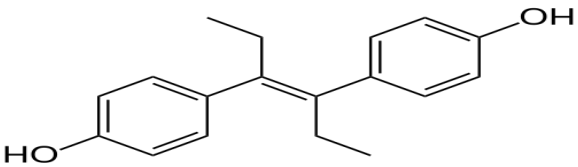
The stereochemistry of methorphan explains the pharmacological action of dextromethorphan and levomethorphan.

Cisplatin and Transplatin



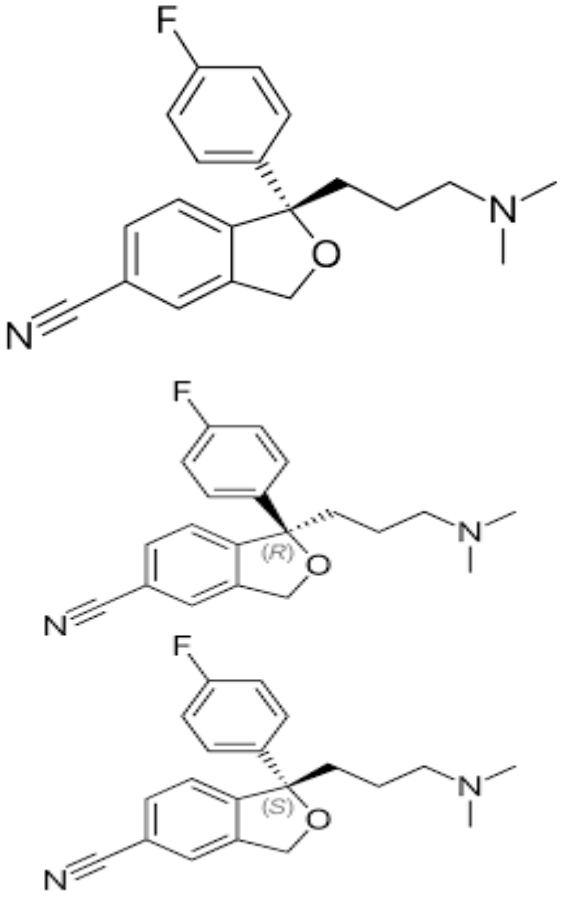
Cisplatin is widely use as chemotherapy drug where as transplatin its transisomer is largely in effective anticancer agent, this difference is largely attributed to their distinct ability to form DNA adducts with cisplatin (cis configuration allowing for more effective) DNA cross-linking, so the cisplatin is antitumor agent and transplatin has minimal to no antitumor activity in most cancer models, these enantiomers difference are in stereochemistry explain the pharmacological action of both isomers.

Cis Diethylstilbestrol and Trans Diethylstilbestrol



Diethylstilbestrol (DES) exists as two stereoisomers, cis and trans. The trans isomer is more biologically active for and cis isomer can convert to the transform invivo contributing to its observed tereogenic effects, both isomers are synthetic estrogens but the transform is more potent due to its structural similarity to estradiol, the transform is binding to estrogen receptors in cells more than cis isomer, where the trans resemble estradiol hormone, also the trans isomer is more stable while the cis isomer tend to convert to the transform.

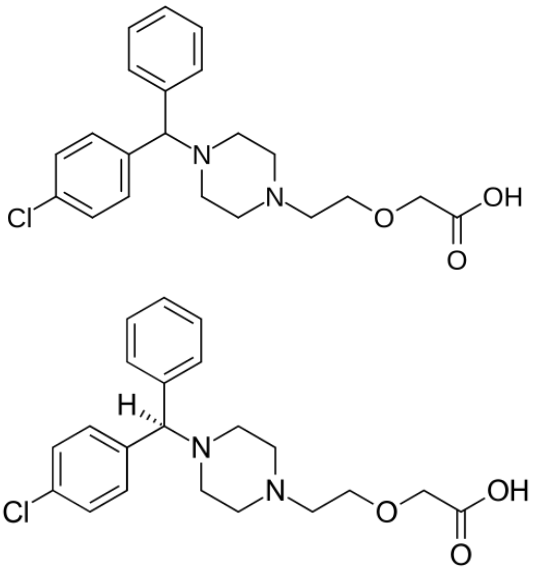
Escitalopram and Citalopram



Escitalopram is the (S)-isomer of citalopram, which is approximately 150 times more potent than the (R)-isomer of citalopram and is responsible (S) for the vast majority of citalopram's clinical activity, with some evidence suggesting the (R)-enantiomer of racemic citalopram actively dampens the activity of escitalopram.

Escitalopram is the (S) enantiomer of citalopram, which is used in the treatment of anxiety and depression for adults and children, while the citalopram ((R) form or racemic mixture) is not used for children, not used for anxiety; hence, the pharmacological action differs between citalopram and escitalopram, and the tolerance by children.

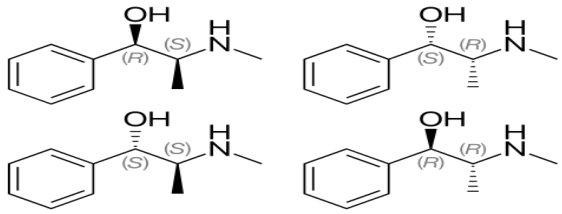
Cetirizine and Levocetirizine



Cetirizine and levocetirizine are both antihistaminic are used to treat allergy symptoms, but levo isomer is active enantiomer of cetirizine i.e. it is a more potent form, levo cetirizine is essentially used half dose of cetirizine and clinical studies suggest it maybe more effective at low doses and potentially loss sedating than cetirizine, where the dose of levocetirizine less than cetirizine.

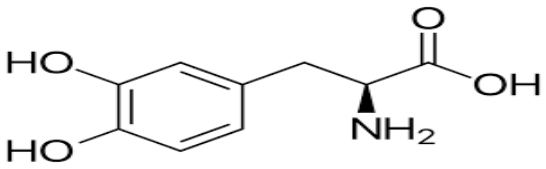
Cetirizine may be a dextro or racemic mixture, but the levo is a pure enantiomer. The stereochemistry of cetirizine explains the potency of the drug, where the dose of levocetirizine is half the dose of cetirizine.

Erythro Ephedrine and Threo Ephedrine



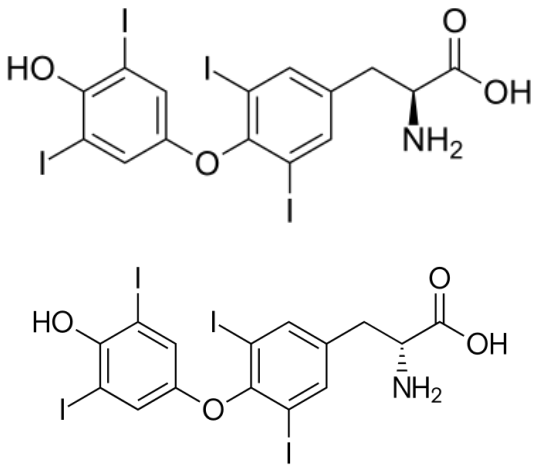
Ephedrine, both natural and synthetic, exists as two pairs of stereo isomers categorized as erythro and threo (pseudo ephedrine) the term of erythro refers to the stereo isomer where the substituents on the chiral carbon are on the same side and the threo ephedrine refers to isomer where the substituents on the two chiral carbons are on opposite side of molecule. Ephedrine is a sympatho-mimetic amine with stimulant properties used for conditions like asthma, high potential and as a decongestant, while both erythro and threo forms have a pharmacological activity, the erythro-form specifically the (-)-ephedrine enantiomer is more commonly used in medical applications like CNS stimulant and treatment of asthma while the pseudo ephedrine used as decongestant agent.

Dopa and Levodopa



Levodopa and dextrodopa are both forms of the molecule 3,4-Dihydroxyphenylalanine, but they differ in their optical activity. L-Dopa is biologically active and used to treat parkinson's disease because it is a precursor to dopamine, which is deficient in parkinson's patients. D-Dopa, the enantiomer of L-Dopa, is biologically inactive due to L-Dopa is able to cross the blood-brain barrier and increase the dopamine in the brain, while the dextro dopa unable to penetrate the blood-brain barrier; hence, the stereochemistry of Dopa explains the mechanism of action and pharmacology of L-Dopa as antiparkinson's agent.

Levothyroxine and Dextrothyroxine



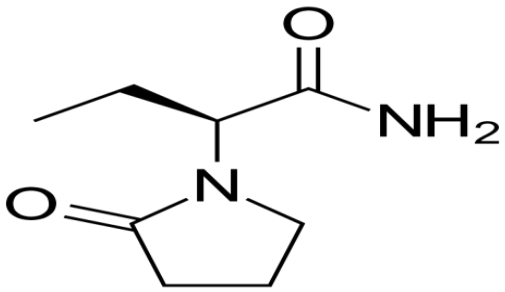
Levothyroxine has pharmacological action when it is used in the treatment of hypothyroidism, where the levo isomer is more active than the dextro isomer.

Dextrothyroxine is used to lower cholesterol levels, particularly triglycerides, in patients with hypercholesterolemia. It can also reduce LDL,

cholesterol and increase HDL.

The stereochemistry of thyroxine explains the activity and the pharmacological action of thyroxine, where the action of levo differs than dextro.

Levetiracetam



Levetiracetam is a drug used to treat epilepsy and it is the (S)-enantiomer of a molecule, the (R)- enantiomer called etiracetam has no anticonvulsant activity while levetiracetam (S-enantiomer) has anticonvulsant activity, levetiracetam is administer as a single enantiomer, where it binds to synaptic vesicle protein (SV2A), which is believed to play a role in neurotransmitter release, this binding is thought to reduce the release of neurotransmitter thus inhibiting the propagation of seizure activity, so the (S)-enantiomer explain the pharmacology of levetiracetam as anticonvulsant agent and the (R)-enantiomer has no anticonvulsant activity.

3. Conclusion

Stereochemistry plays a critical role in determining the pharmacological efficacy, safety, and overall therapeutic profile of pharmaceutical agents. The spatial arrangement of atoms within a drug molecule directly influences its interaction with biological targets such as receptors, enzymes, and transporters. This research highlights several clinically relevant examples where enantiomers and geometric isomers exhibit significantly different pharmacodynamic and pharmacokinetic profiles, emphasizing the importance of stereoselectivity in drug design and clinical application.

From the antitussive and opioid effects of dextromethorphan and levomethorphan, to the selective anticancer activity of cisplatin over transplatin, and the improved potency and safety of drugs like escitalopram, levocetirizine, and levetiracetam, it is evident that the stereochemical configuration dictates both the mechanism of action and therapeutic outcomes. Furthermore, the ability of only certain enantiomers, such as levodopa, to cross physiological barriers and exert their intended effect underscores the necessity for stereochemically pure formulations in achieving optimal treatment responses.

As pharmaceutical science advances, greater emphasis must be placed on chiral synthesis, enantioselective drug development, and precise stereochemical characterization to ensure the efficacy and safety of future medications. Understanding and leveraging stereochemistry is not merely a chemical concern but a clinical imperative that shapes modern pharmacotherapy.

References

A Ibrahim, HM Sakr, RR Ayyad, & MM Khalifa. (2022). Design, synthesis, in-vivo anti-diabetic activity, in-vitro α-glucosidase inhibitory activity and molecular docking studies of some quinazolinone derivatives. *ChemistrySelect, 7*(14), e202104590.

AA El-Helby, MK Ibrahim, AA Abdel-Rahman, RRA Ayyad, MA Menshawy, et al. (2009). Synthesis, molecular modeling and anticonvulsant activity of benzoxazole derivatives. *Al-Azhar Journal of Pharmaceutical Sciences, 40*, 252–270.

AA Elhelby, RR Ayyad, & MF Zayed. (2011). Synthesis and biological evaluation of some novel quinoxaline derivatives as anticonvulsant agents. *Arzneimittelforschung, 61*(07), 379–381.

AAM Abdel-Aziz, AS El-Azab, AM Alanazi, YA Asiri, IA Al-Suwaidan, et al. (2016). Synthesis and potential antitumor activity of 7-(4-substituted piperazin-1-yl)-4-oxoquinolines based on ciprofloxacin and norfloxacin scaffolds: In silico studies. *Journal of Enzyme Inhibition and Medicinal Chemistry, 31*(5), 796–809.

AGA El-Helby, H Sakr, RR Ayyad, HA Mahdy, MM Khalifa, & A Belal, et al. (2022). Design, synthesis, molecular modeling, in vivo studies and anticancer activity evaluation of new phthalazine derivatives as potential DNA intercalators and topoisomerase II inhibitors. *Bioorganic Chemistry, 103*, 104233.

AGA El-Helby, H Sakr, RRA Ayyad, K El-Adl, MM Ali, & F Khedr. (2018). Design,

synthesis, in vitro anti-cancer activity, ADMET profile and molecular docking of novel triazolo[3,4-a]phthalazine derivatives targeting VEGFR-2 enzyme. *Anti-Cancer Agents in Medicinal Chemistry, 18*(8), 1184–1196.

AGA El-Helby, RR Ayyad, HM Sakr, AS Abdelrahim, K El-Adl, & FS Sherbiny, et al. (2017). Design, synthesis, molecular modeling and biological evaluation of novel 2,3-dihydrophthalazine-1,4-dione derivatives as potential anticonvulsant agents. *Journal of Molecular Structure, 1130*, 333–351.

AGA El-Helby, RRA Ayyad, H Sakr, K El-Adl, MM Ali, & F Khedr. (2017). Design, synthesis, molecular docking, and anticancer activity of phthalazine derivatives as VEGFR-2 inhibitors. *Archiv der Pharmazie, 350*(12), 1700240.

AGA El-Helby, RRA Ayyad, K El-Adl, & A Elwan. (2017). Quinoxalin-2(1H)-one derived AMPA-receptor antagonists: Design, synthesis, molecular docking and anticonvulsant activity. *Medicinal Chemistry Research, 26*, 2967–2984.

AGA El-Helby, RRA Ayyad, K El-Adl, & H Elkady. (2018). Phthalazine-1,4-dione derivatives as non-competitive AMPA receptor antagonists: Design, synthesis, anticonvulsant evaluation, ADMET profile and molecular docking. *Molecular Diversity, 23*, 283–298.

AGA El-Helby, RRA Ayyad, K El-Adl, H Sakr, AA Abd-Elrahman, & IH Eissa, et al. (2016). Design, molecular docking and synthesis of some novel 4-acetyl-1-substituted-3,4-dihydroquinoxalin-2(1H)-one derivatives for anticonvulsant evaluation as AMPA-receptor antagonists. *Medicinal Chemistry Research, 25*, 3030–3046.

AGA El-Helby, RRA Ayyad, MF Zayed, HS Abulkhair, H Elkady, & K El-Adl. (2019). Design, synthesis, in silico ADMET profile and GABA-A docking of novel phthalazines as potent anticonvulsants. *Archiv der Pharmazie, 352*(5), 1800387.

AM Alaa, AS El-Azab, LA Abou-Zeid, KEH ElTahir, NI Abdel-Aziz, et al. (2016). Synthesis, anti-inflammatory, analgesic and COX-1/2 inhibition activities of anilides based on 5,5-diphenylimidazolidine-2,4-dione scaffold: Molecular docking studies. *European Journal of Medicinal Chemistry, 115*, 121–131.

AM Alaa, LA Abou-Zeid, KEH ElTahir, RR Ayyad, AA Magda, & AS El-Azab. (2016). Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4(3H)-quinazolinones. *European Journal of Medicinal Chemistry, 121*, 410–421.

AM Alanazi, AAM Abdel-Aziz, TZ Shawer, RR Ayyad, & AM Al-Obaid, et al. (2016). Synthesis, antitumor and antimicrobial activity of some new 6-methyl-3-phenyl-4(3H)-quinazolinone analogues: In silico studies. *Journal of Enzyme Inhibition and Medicinal Chemistry, 31*(5), 721–735.

AS El-Azab, AM Alaa, RR Ayyad, M Ceruso, & CT Supuran. (2016). Inhibition of carbonic anhydrase isoforms I, II, IV, VII and XII with carboxylates and sulfonamides incorporating phthalimide/phthalic anhydride scaffolds. *Bioorganic & Medicinal Chemistry, 24*(1), 20–25.

Ayyad, Rezk R., et al. (2024). Overview on some drugs act on DNA and RNA other than anti-viral drugs—The direct cholinomimetics and cholinergic blocking agents depend on stereo specificity of cholinergic receptors. *Current Research in Medical Sciences, 3*(3), 20–27.

Ayyad, Rezk R., et al. (2024). The direct cholinomimetics and cholinergic blocking agents depend on stereo specificity of cholinergic receptors. *Current Research in Medical Sciences, 3*(2), 1–7.

E Nassar, YA El-Badry, AMM Eltoukhy, & RR Ayyad. (2016). Synthesis and antiproliferative activity of 1-(4-(1H-indol-3-yl)-6-(4-methoxyphenyl) pyrimidin-2-yl) hydrazine and its pyrazolopyrimidine derivatives. *Med Chem (Los Angeles), 6*, 224–233.

H M Sakr, R R Ayyad, K Mahmoud, A M Mansour, & G Ahmed. (2021). Design, synthesis of analgesics and anticancer of some new derivatives of benzimidazole. *International Journal of Organic Chemistry, 11*(03), 144–169.

H Mahdy, & M Shaat. (2022). Recent advances in

drugs targeting protein kinases for cancer therapy. *Al-Azhar Journal of Pharmaceutical Sciences*, *66*(2), 56–86.

H Sakr, I Otify, RR Ayyad, & A Elwan. (2023). Vegfer-2 inhibitors and quinazoline-based anticancer agents. *Al-Azhar Journal of Pharmaceutical Sciences*, *68*(2), 111–129.

H Sakr, RR Ayyad, AA El-Helby, MM Khalifa, & HA Mahdy. (2021). Discovery of novel triazolophthalazine derivatives as DNA intercalators and topoisomerase II inhibitors. *Archiv der Pharmazie*, *354*(6), 2000456.

IA Al-Suwaidan, AAM Abdel-Aziz, TZ Shawer, RR Ayyad, & AM Alanazi, et al. (2015). Synthesis, antitumor activity and molecular docking study of some novel 3-benzyl-4(3H)-quinazolinone analogues. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *31*(1), 78–89.

IA Osman, RR Ayyad, & HA Mahdy. (2022). New pyrimidine-5-carbonitrile derivatives as EGFR inhibitors with anticancer and apoptotic activities: Design, molecular modeling and synthesis. *New Journal of Chemistry*, *46*(24), 11812–11827.

IH Eissa, AM Metwaly, A Belal, ABM Mehany, RR Ayyad, & K El-Adl, et al. (2019). Discovery and antiproliferative evaluation of new quinoxalines as potential DNA intercalators and topoisomerase II inhibitors. *Archiv der Pharmazie*, *352*(11), 1900123.

K El-Adl, AGA El-Helby, H Sakr, RR Ayyad, HA Mahdy, & M Nasser, et al. (2020). Design, synthesis, molecular docking, anticancer evaluations, and in silico pharmacokinetic studies of novel 5-[(4-chloro/2,4-dichloro)benzylidene] thiazolidine-2,4-dione derivatives as VEGFR-2 inhibitors. *Archiv der Pharmazie*, *354*(2), 2000279.

K El-Adl, AGA El-Helby, RR Ayyad, HA Mahdy, MM Khalifa, & HA Elnagar, et al. (2020). Design, synthesis, and anti-proliferative evaluation of new quinazolin-4(3H)-ones as potential VEGFR-2 inhibitors. *Bioorganic & Medicinal Chemistry*, *29*, 115872.

M Al Ward, AE Abdallah, M Zayed, R Ayyad, & M El-Zahabi. (2024). New immunomodulatory anticancer quinazolinone based thalidomide analogs: Design, synthesis and biological evaluation. *Future Medicinal Chemistry*, *16*(23), 2523–2533.

M Salem, R Ayyad, & H Sakr. (2022). Design and synthesis of some new oxadiazole derivatives as anticancer agents. *International Journal of Organic Chemistry*, *12*(02), 64–74.

MA Mohamed, RR Ayyad, TZ Shawer, AM Alaa, & AS El-Azab. (2016). Synthesis and antitumor evaluation of trimethoxyanilides based on 4(3H)-quinazolinone scaffolds. *European Journal of Medicinal Chemistry*, *112*, 106–113.

MF Zayed, & RR Ayyad. (2012). Some novel anticonvulsant agents derived from phthalazinedione. *Arzneimittelforschung*, *62*(11), 532–536.

MK Ibrahim, AA Abd-Elrahman, RRA Ayyad, K El-Adl, & AM Mansour, et al. (2013). Design and synthesis of some novel 2-(3-methyl-2-oxoquinoxalin-1(2H)-yl)-N-(4 -(substituted)phenyl) acetamide derivatives for biological evaluation as anticonvulsant agents. *Bulletin of Faculty of Pharmacy, Cairo University*, *51*(1), 101–111.

MK Ibrahim, AEA El-Helby, AH Ghiaty, AH Biomy, & AA Abd-El Rahman, et al. (2009). Modeling, synthesis and antihyperglycemic activity of novel quinazolinones containing sulfonylurea. *Journal of Biological Pharmaceutical Sciences*, *7*(1).

MM Khalifa, HM Sakr, A Ibrahim, AM Mansour, & RR Ayyad. (2022). Design and synthesis of new benzylidene-quinazolinone hybrids as potential anti-diabetic agents: In vitro α-glucosidase inhibition, and docking studies. *Journal of Molecular Structure*, *1250*, 131768.

MMS Al Ward, AE Abdallah, MF Zayed, RR Ayyad, & MA El-Zahabi. (2024). Design, synthesis and biological evaluation of newly triazolo-quinoxaline based potential immunomodulatory anticancer molecules. *Journal of Molecular Structure*, *1298*, 137041.

R Ayyad, H Sakr, & A Gaafer. (2022). Design and synthesis of new compounds derived from phenyl hydrazine and different aldehydes as anticancer agents. *International Journal of Organic Chemistry*, *12*(1), 28–39.

R Ayyad. (2012). Synthesis and biological evaluation of novel iodophthalazinedione derivatives as anticonvulsant agents. *Al-Azhar Journal of Pharmaceutical Sciences*,

45(1), 1–13.

R Ayyad. (2014). Synthesis and anticonvulsant activity of 6-iodo phthalazinedione derivatives. *Al-Azhar Journal of Pharmaceutical Sciences, 50*(2), 43–54.

RA Ayyad, HM Sakr, & KM El-Gamal. (n.d.). Design, synthesis, computer modeling and analgesic activity of some new disubstituted quinazolin-4(3H)-ones. *Med Chem, 6*(5), 299–305.

RR Ayyad, AM Mansour, AM Nejm, YAA Hassan, & AR Ayyad. (2024). Stereo selectivity of histaminic receptors play an important role of anti-histaminic activity. *Current Research in Medical Sciences, 3*(1), 10–17.

RR Ayyad, AM Mansour, AM Nejm, YAA Hassan, & AR Ayyad. (2025). Esterification of many drugs causes its prolonged action due to increase lipid solubility and store in fatty tissues. *Current Research in Medical Sciences, 4*(2), 10–15.

RR Ayyad, AM Nejm, & AR Ayyad. (2023). The activity of some antibiotics depend on stereochemistry of them (its structure). *Journal of Progress in Engineering and Physical Science, 2*(2), 5–7.

RR Ayyad, AM Nejm, & AR Ayyad. (2023). The isomers of some drugs one effective and the other is toxic or ineffective. *Current Research in Medical Sciences, 2*(2), 58–62.

RR Ayyad, AM Nejm, ELT Elbahat, AM Elnagar, & MA Aljazar, et al. (2023). The configuration of some hormonal compounds play an important role in pharmacological action (agonist, antagonist, active, more active). *Journal of Progress in Engineering and Physical, 2*(3).

RR Ayyad, AM Nejm, YAA Hassan, & AR Ayyad, et al. (2024). Repair of destroyed liver cells or protection liver cells from destruction by silymarin and minor concentration of vitamin E and vitamin K. *Journal of Progress in Engineering and Physical*.

RR Ayyad, AM Nejm, YAA Hassan, & AR Ayyad. (2023). Mechanism of action of many drugs depend on enzyme inhibition. *Current Research in Medical Sciences, 2*(4), 1–9.

RR Ayyad, AM Nejm, YAA Hassan, & AR Ayyad. (2023). The lipid solubility of most drugs play important role of its pharmacological action and duration of action. *Journal of Progress in Engineering and Physical Science, 2*(4), 1–6.

RR Ayyad, AM Nejm, YH Abdelaleem, & AR Ayyad. (2023). Hydrophobicity, transport and target sites of action are important for the activity of many drugs. *Current Research in Medical Sciences, 2*(3), 15–19.

RR Ayyad, HM Sakr, KM El-Gamal, IH Eissa, A HA, AS Tita, & FF Sherbini, et al. (2017). Anti-inflammatory, proton pump inhibitor and synthesis of some new benzimidazole derivatives. *Der Chemica Sinica, 8*(1), 184–197.

RRA Ayyad, H Sakr, & K El-Gamal. (2016). Synthesis, modeling and anticonvulsant activity of some phthalazinone derivatives. *American Journal of Organic Chemistry, 6*(1), 29–38.

T Al-Warhi, AM El Kerdawy, N Aljaeed, OE Ismael, & RR Ayyad, et al. (2020). Synthesis, biological evaluation and in silico studies of certain oxindole–indole conjugates as anticancer CDK inhibitors. *Molecules, 25*(9), 2031.

T Al-Warhi, H Almahli, RM Maklad, ZM Elsayed, & MA El Hassab, et al. (2023). 1-Benzyl-5-bromo-3-hydrazonoindolin-2-ones as novel anticancer agents: Synthesis, biological evaluation and molecular modeling insights. *Molecules, 28*(7), 3203.

WM Eldehna, MF Abo-Ashour, T Al-Warhi, ST Al-Rashood, & A Alharbi, et al. (2021). Development of 2-oxindolin-3-ylidene-indole-3-carbohydrazide derivatives as novel apoptotic and anti-proliferative agents towards colorectal cancer cells. *Journal of Enzyme Inhibition and Medicinal Chemistry, 36*(1), 320–329.

WM Eldehna, R Salem, ZM Elsayed, T Al-Warhi, HR Knany, & RR Ayyad, et al. (2021). Development of novel benzofuran-isatin conjugates as potential antiproliferative agents with apoptosis inducing mechanism in colon cancer. *Journal of Enzyme Inhibition and Medicinal Chemistry, 36*(1), 1423–1434.

WM Eldehna, SM Abou-Seri, AM El Kerdawy, RR Ayyad, & AM Hamdy, et al. (2016). Increasing the binding affinity of VEGFR-2 inhibitors by extending their hydrophobic interaction with the active site: Design, synthesis and biological evaluation of

1-substituted-4-(4-methoxybenzyl) phthalazine derivatives. *European Journal of Medicinal Chemistry, 113*, 50–62.

Current Research in Medical Sciences
ISSN 2958-0390
www.paradigmpress.org/crms
Volume 5 Number 1 January 2026

Linking Synaptic Pathology to Network-Level Reorganization in Neurological Disease

Ruben Smit[1]

[1] Vrije Universiteit Amsterdam, Amsterdam, Netherlands
Correspondence: Ruben Smit, Vrije Universiteit Amsterdam, Amsterdam, Netherlands.

doi:10.63593/CRMS.2026.01.04

Abstract

Neurological diseases are increasingly recognized as disorders of distributed brain networks rather than consequences of isolated focal lesions, yet large-scale dysfunction originates in microscopic alterations of synaptic structure and function that propagate across hierarchical levels of neural organization. This paper develops a multilevel theoretical framework linking synaptic pathology to network-level reorganization by tracing how structural synaptic loss, functional transmission abnormalities, and disrupted plasticity reshape microcircuit dynamics through altered excitation–inhibition balance, impaired interneuron timing, and disturbed oscillatory coordination. These microcircuit changes propagate via long-range projections, leading to modifications in functional connectivity, modular architecture, and large-scale network dynamics. The model incorporates threshold effects and nonlinear amplification to explain abrupt transitions into pathological states such as hypersynchrony, network slowing, and instability. Cross-disease comparison across epilepsy, Alzheimer's disease, and Parkinson's disease demonstrates how distinct synaptic perturbations produce characteristic network phenotypes while following a common hierarchical cascade. By conceptualizing disease progression as a dynamic transformation from synaptic disturbance to consolidated network reconfiguration, this framework positions network remodeling as the core systems-level expression of neurological pathology and underscores the necessity of analyzing brain disorders across synaptic, circuit, and distributed network scales.

Keywords: synaptic pathology, network reorganization

1. Introduction

The nervous system is structured as a deeply layered biological system in which events at one scale influence organization at every other scale. At the molecular level, receptor distributions, ion channel densities, and intracellular signaling cascades shape the strength and timing of synaptic transmission. At the cellular level, neurons integrate thousands of synaptic inputs to generate precisely timed output patterns. These neurons are embedded within microcircuits composed of excitatory and inhibitory elements arranged in recurrent architectures. Microcircuits are not isolated computational units. They are components of broader functional networks that span cortical and subcortical territories, linking sensory processing areas with associative regions and motor output systems. Large-scale networks maintain coherent behavior through

coordinated oscillatory activity and structured connectivity patterns.

This hierarchical arrangement is not simply anatomical. It is dynamical. Each level operates with its own temporal and spatial scales. Synaptic events unfold within milliseconds and micrometers. Microcircuit interactions extend across millimeters and tens of milliseconds. Network-level coordination may involve distributed regions interacting across centimeters and hundreds of milliseconds. Despite these differences, the levels are tightly coupled. Synaptic efficacy determines neuronal firing probability. Neuronal firing shapes circuit oscillations. Circuit oscillations regulate long-range synchronization. The entire system behaves as a nested set of feedback loops in which small perturbations can alter global states.

Such coupling explains why neurological disease rarely remains confined to a microscopic abnormality. A modest reduction in synaptic density can alter input integration. Slight shifts in excitatory or inhibitory balance can modify spike timing. Changes in timing disrupt local synchrony. Altered synchrony affects communication between distant brain regions. The result is not merely a local deficit but a reorganization of activity patterns across distributed systems. Clinical symptoms often reflect this systems-level transformation rather than the original microscopic lesion.

For much of the twentieth century, neurological disorders were conceptualized through lesion-based models. Observations from stroke, tumor resection, and traumatic injury supported the idea that damage to a discrete anatomical region produces a predictable functional deficit. This approach clarified the localization of language, motor control, and sensory processing. It provided a powerful framework for correlating structure and function. Yet many neurological conditions do not conform neatly to focal localization. Epileptic seizures propagate across hemispheres. Cognitive decline in neurodegenerative disease correlates poorly with the size of any single lesion. Movement disorders involve distributed circuit abnormalities that extend beyond identifiable structural damage.

The limitations of focal models have become increasingly evident with advances in neuroimaging and electrophysiology. Functional magnetic resonance imaging reveals coherent resting-state networks that persist in the absence of overt tasks. Diffusion imaging demonstrates that white matter pathways form highly organized structural connectomes with hub regions and modular organization. Electrophysiological recordings show that brain function depends on coordinated oscillatory dynamics across spatial scales. Within this network-oriented framework, pathology appears not only as tissue loss but also as altered connectivity strength, abnormal synchronization, and shifts in network topology. Disease becomes a disturbance of interactions rather than solely a matter of localized destruction.

This shift in perspective invites reconsideration of the origin of pathological states. If large-scale dysfunction reflects altered connectivity and dynamics, then the initiating perturbation must be traced to the level where communication is first encoded. Synapses represent this fundamental site. They determine how information flows from one neuron to another. They regulate plasticity, enabling adaptation or consolidation of activity patterns. They maintain the balance between excitation and inhibition that stabilizes circuit activity. When synaptic structure or function is disrupted, the computational properties of neurons change. Altered neuronal responses reshape microcircuit organization. Microcircuit imbalance modifies oscillatory coordination. Distributed networks then reorganize according to new patterns of effective connectivity.

Neurological disease cannot therefore be fully explained by identifying a damaged region in isolation. The visible lesion may be only one manifestation of a broader dynamic transformation. Synaptic pathology often precedes overt neuronal death or gross anatomical change. Subtle modifications in receptor composition, synaptic density, or inhibitory control can accumulate silently. Once critical thresholds are crossed, these local disturbances amplify through recurrent loops and network hubs, producing emergent dysfunction at the systems level. The clinical phenotype reflects this emergent network state.

The central argument of this essay is that synaptic pathology constitutes the initial perturbation in many neurological diseases, yet its true impact lies in its capacity to reorganize networks. Synaptic alterations serve as the

starting point of a cascade that progresses from molecular change to circuit imbalance and finally to distributed network reconfiguration. Network-level phenotypes are not secondary epiphenomena. They are the structural and dynamical expression of accumulated synaptic disruption. A comprehensive understanding of neurological disease requires following this trajectory across hierarchical scales, recognizing that the brain operates as an integrated system in which microscopic events and macroscopic states are inseparably linked.

2. Synaptic Pathology as the Initial Peturbation

Synapses are the fundamental units through which neurons communicate, adapt, and stabilize network function. Every perception, movement, memory trace, and behavioral output depends on the reliability and plasticity of synaptic transmission. Because synapses regulate the probability, timing, and strength of neuronal firing, even subtle disturbances at this level can reshape information flow across the nervous system. Synaptic pathology represents the earliest and most granular form of disruption in many neurological conditions. It often precedes neuronal loss, macroscopic atrophy, or overt structural lesions. The perturbation begins at the point where signals are exchanged and where plastic changes are encoded.

Structural synaptic alterations constitute one major dimension of this pathology. Synaptic loss reduces the number of available communication points between neurons. A reduction in spine density on dendrites diminishes the integrative capacity of postsynaptic cells. Changes in dendritic spine morphology alter the surface area available for receptor insertion and modify electrical compartmentalization within dendrites. Thin spines associated with plastic states may disappear, while mushroom spines linked to stable connections may shrink or fragment. Presynaptic terminals may undergo degeneration, leading to decreased vesicle availability and altered release probability. Active zone organization may deteriorate, disrupting the precise alignment between neurotransmitter release sites and postsynaptic receptor clusters.

Structural abnormalities are not limited to overt synapse elimination. Subtle rearrangements of synaptic architecture can produce disproportionate functional consequences. Altered clustering of postsynaptic density proteins affects receptor anchoring and signaling cascades. Cytoskeletal instability influences spine motility and stabilization. Disturbances in axonal transport impair delivery of synaptic components, leading to gradual weakening of synaptic contacts. Because synaptic density in many cortical areas is exceptionally high, small percentage losses can translate into large reductions in computational diversity and redundancy.

Functional synaptic dysfunction adds another layer of perturbation. Neurotransmitter release may become inconsistent due to presynaptic calcium handling abnormalities. Postsynaptic receptor sensitivity may decline because of altered phosphorylation states or receptor internalization. Changes in subunit composition of glutamate receptors modify conductance properties and kinetics. Inhibitory transmission may weaken through reduced gamma aminobutyric acid synthesis or impaired receptor responsiveness. These changes alter the balance between excitation and inhibition, a balance that is central to stable neural computation.

The concept of excitation and inhibition balance reflects more than overall firing rate. It captures the dynamic interplay between excitatory pyramidal neurons and inhibitory interneurons that sculpt temporal precision. Excess excitation increases network gain and enhances the likelihood of runaway activity. Excess inhibition suppresses responsiveness and reduces information throughput. Balanced conditions allow selective amplification of relevant signals while suppressing noise. Synaptic dysfunction that shifts this equilibrium changes the operating point of circuits. Networks may become hyperexcitable or excessively dampened, each state carrying distinct pathological implications.

Synaptic pathology also disrupts mechanisms of plasticity. Long term potentiation and long term depression regulate synaptic strength in response to experience. These mechanisms depend on tightly controlled calcium dynamics, receptor trafficking, and intracellular signaling pathways. Impaired potentiation reduces the capacity to encode new information. Impaired depression prevents removal of maladaptive or redundant connections. Aberrant stabilization of potentiated synapses may reinforce pathological activity patterns. Disruption of homeostatic

plasticity impairs the ability of neurons to adjust synaptic strength in response to prolonged changes in activity. Without homeostatic correction, small imbalances accumulate and destabilize circuits.

Temporal aspects of synaptic dysfunction are equally significant. Synapses operate within millisecond precision. Spike timing dependent plasticity relies on exact temporal relationships between pre and postsynaptic firing. Distortion of these relationships alters learning rules and connectivity refinement. Changes in short term plasticity affect synaptic filtering properties, influencing how neurons respond to high frequency or low frequency input streams. Such alterations modify the temporal structure of information transmission before any structural degeneration becomes visible.

Metabolic and molecular stressors often converge at synapses. Mitochondrial dysfunction impairs local energy supply, compromising vesicle recycling and receptor trafficking. Oxidative stress damages synaptic proteins and lipids. Abnormal protein aggregation interferes with synaptic signaling complexes. Inflammatory mediators alter neurotransmitter release and receptor sensitivity. These factors contribute to a microenvironment in which synaptic reliability declines gradually. Because synapses are highly dynamic and metabolically active, they are particularly vulnerable to such disturbances.

Synaptic pathology represents an initial perturbation not simply because it occurs early, but because it modifies the fundamental parameters governing neuronal interaction. The strength, timing, and probability of communication between neurons define the architecture of circuit computation. Once these parameters shift, microcircuits reorganize in response. Compensatory mechanisms may transiently mask dysfunction, yet the altered baseline persists. Recurrent networks amplify minor deviations through feedback loops. Hub neurons that integrate multiple inputs become especially sensitive to synaptic perturbation. Over time, the cumulative effect of altered synaptic interactions reshapes activity patterns across broader networks.

3. Microcircuit-Level Consequences

Microcircuits represent the intermediate layer between individual synapses and distributed brain networks. They consist of tightly interconnected excitatory principal neurons and diverse classes of inhibitory interneurons arranged in recurrent architectures. Within cortical and subcortical regions, these microcircuits perform local computations that transform input streams into temporally structured output signals. Their function depends on precise synaptic weighting, balanced excitation and inhibition, and coordinated oscillatory activity. When synaptic pathology alters these parameters, microcircuit dynamics shift in systematic ways. The consequences at this level form the bridge between microscopic disruption and macroscopic reorganization.

Interneuron dysfunction occupies a central position in microcircuit disturbance. Inhibitory interneurons regulate gain control, timing precision, and spatial confinement of excitation. Parvalbumin-positive interneurons synchronize pyramidal cell firing through fast perisomatic inhibition. Somatostatin-expressing interneurons shape dendritic integration and control distal excitatory inputs. Vasoactive intestinal peptide interneurons modulate inhibitory hierarchies by disinhibiting specific neuronal populations. When synaptic pathology weakens inhibitory transmission or reduces interneuron excitability, the delicate balance that constrains excitation deteriorates. Local networks may exhibit excessive firing variability, broadened receptive fields, or unstable amplification of minor inputs.

Loss of inhibitory precision does not simply increase overall activity. It alters temporal coordination. Inhibition normally sculpts the exact window during which excitatory neurons can fire. Reduced inhibitory efficacy widens this temporal window, allowing spikes to occur with less constraint. Spike timing variability increases. Population responses become less coherent. Alternatively, certain pathological conditions may produce excessive inhibitory tone in specific microcircuits, suppressing responsiveness and narrowing dynamic range. Both hyperexcitability and excessive suppression represent imbalanced states that distort computational output.

Microcircuit-level imbalance often manifests through altered oscillatory dynamics. Rhythmic activity emerges from reciprocal interactions between excitatory and inhibitory neurons. Gamma oscillations depend on fast inhibitory feedback loops that synchronize pyramidal cell

ensembles. Beta rhythms reflect interactions between cortical and subcortical loops involved in motor and cognitive control. Theta oscillations coordinate long-range communication and memory-related processes. When synaptic dysfunction modifies inhibitory timing or excitatory drive, oscillatory frequency and coherence shift. Gamma power may decline due to impaired fast-spiking interneuron coordination. Beta oscillations may become excessively persistent, reducing flexibility of motor circuits. Theta rhythms may lose phase stability, weakening cross-regional coupling.

Oscillatory disturbances carry significant computational implications. Rhythms organize information flow by structuring periods of excitability and inhibition. They enable phase coding, in which the timing of spikes relative to oscillatory cycles conveys information. Disrupted rhythms degrade this coding scheme. Neurons may fire outside optimal phase windows, reducing communication efficiency. The breakdown of local rhythmic stability compromises the reliability of signals transmitted to distant regions.

Another consequence of synaptic perturbation at the microcircuit level is the degradation of signal-to-noise ratio. Healthy microcircuits amplify relevant inputs while suppressing background fluctuations. Balanced excitation and inhibition ensure selective responsiveness. When synaptic weights become unstable, spontaneous activity may rise, increasing background noise. Alternatively, weakened excitatory connections may reduce responsiveness to meaningful input. In both scenarios, discriminability declines. Temporal coding precision weakens as variability in spike timing increases. The reliability of population coding deteriorates, impairing the capacity of circuits to represent sensory, cognitive, or motor information accurately.

Microcircuit architecture also determines the propagation of activity. Recurrent excitatory loops provide amplification, while inhibitory feedback prevents runaway excitation. If recurrent excitation becomes dominant due to synaptic strengthening or loss of inhibitory control, microcircuits may enter self-sustaining activity states. These states can manifest as persistent firing or localized hypersynchrony. Such patterns form the substrate for pathological spreading in conditions characterized by network instability. In contrast, excessive synaptic weakening may fragment recurrent loops, leading to reduced integration and functional isolation of neuronal ensembles.

Plastic adaptation at the microcircuit level may initially compensate for synaptic disruption. Remaining synapses may strengthen to offset loss. Inhibitory circuits may adjust firing thresholds to restore balance. Homeostatic scaling mechanisms attempt to normalize overall activity levels. Yet compensation alters baseline connectivity patterns. Strengthened connections may reorganize ensemble structure. Adjusted inhibitory thresholds may change oscillatory frequencies. Over time, these compensatory shifts can become maladaptive if they overshoot or stabilize abnormal configurations.

Spatial organization within microcircuits further influences the impact of synaptic pathology. Neurons are arranged in layered and columnar structures with specific connectivity motifs. Disruption within one layer can propagate vertically and horizontally. Layer-specific synaptic loss may impair feedforward processing while sparing feedback loops, or vice versa. Altered connectivity within microcolumns may disturb feature selectivity in sensory cortex. These localized disruptions contribute to larger-scale network reorganization by modifying the output characteristics of each affected region.

The microcircuit level thus serves as a critical amplification stage. Synaptic pathology changes the parameters of neuronal interaction. These altered parameters reshape oscillatory coordination, inhibitory control, and ensemble organization. Local disturbances generate new dynamic regimes that can propagate through long-range connections. Microcircuits translate microscopic abnormalities into patterns of activity that influence distributed networks. Understanding this intermediate stage clarifies how subtle synaptic alterations evolve into system-level dysfunction.

4. Emergence of Network-Level Reorganization

Network-level reorganization represents the stage at which local circuit disturbances become embedded in large-scale patterns of communication across the brain. At this level, pathology is expressed not only as altered activity within a single region but as systematic changes in how regions interact, coordinate, and integrate information. The brain operates as a

complex network characterized by modular organization, hub structure, and dynamic coupling across spatial scales. When synaptic and microcircuit perturbations persist, they reshape the topology and dynamics of this network architecture.

Functional connectivity refers to the statistical association between activity patterns in spatially separated regions. These associations reflect coordinated fluctuations that arise from structural pathways and shared inputs. Synaptic disturbances alter neuronal firing properties, which in turn modify the temporal structure of signals transmitted along long-range projections. As these altered signals propagate, correlations between regions shift. Some areas may display increased synchrony due to shared hyperexcitable input. Others may exhibit reduced coherence because weakened output from one region fails to entrain its targets.

Hyperconnectivity often emerges in early stages of disease or in response to focal disruption. Regions adjacent to an affected node may increase coupling in an attempt to stabilize information flow. Hubs that normally coordinate integration across modules may exhibit elevated centrality, reflecting compensatory recruitment. This increase in connectivity can temporarily sustain performance by redistributing processing load. Yet sustained hyperconnectivity increases metabolic demand and may amplify noise, rendering the system less efficient over time.

Disconnection represents the opposite pattern. Reduced synaptic integrity within a region diminishes the fidelity of its outgoing signals. Downstream areas receive degraded input and may reduce reciprocal coupling. Modules that once communicated effectively can fragment into partially isolated subcomponents. Disconnection disrupts integration of information across sensory, cognitive, and motor domains. Behavioral symptoms frequently reflect this fragmentation rather than localized tissue damage.

Network modules, defined as clusters of densely interconnected nodes, may undergo reconfiguration. Boundaries between modules can blur if abnormal synchronization binds previously distinct systems. Alternatively, modules may become more segregated if weakened long-range connections fail to maintain integration. This shift between integration and segregation alters the balance that supports adaptive cognition. Efficient brain function requires both specialized processing within modules and coordinated communication across modules. Reorganization disturbs this balance.

Hub regions are particularly important in this process. Hubs possess high degree and high centrality, enabling them to coordinate communication across the network. They are metabolically demanding and structurally connected to multiple modules. Synaptic pathology affecting hubs has disproportionate consequences. Reduced hub efficiency diminishes global integration. Excessive hub synchronization can impose rigid patterns on distributed circuits. Cascading effects propagate along hub-centered pathways, transforming local abnormalities into widespread dysfunction.

Structural network remodeling accompanies functional changes. White matter tracts that support long-range communication may undergo degeneration due to axonal damage or reduced trophic support. Loss of myelin integrity slows conduction velocity and disrupts temporal coordination between regions. Altered timing modifies phase relationships, weakening oscillatory coupling. Structural degradation consolidates patterns of functional disconnection that may have originated from synaptic instability.

Plastic responses also occur at the structural level. Surviving pathways may strengthen through activity-dependent mechanisms. Axonal sprouting can create new connections that bypass damaged regions. Such rewiring alters the topology of the network. Newly formed connections may restore certain communication routes while introducing atypical coupling patterns. The emergent architecture may differ substantially from the original configuration, reflecting adaptation under pathological constraints.

Over time, repeated activity within reorganized pathways stabilizes the new configuration. Hebbian mechanisms reinforce frequently coactivated nodes. Reduced use of weakened connections leads to further pruning. The network gradually transitions into a different attractor state characterized by altered connectivity strength and topology. Once this state stabilizes, it may persist even if the initial

synaptic disturbance is partially corrected. The system becomes organized around a new baseline.

Compensatory reorganization reflects attempts to preserve function under altered conditions. Increased recruitment of secondary regions during cognitive or motor tasks exemplifies this adaptive strategy. Strengthening of parallel pathways can distribute computational load. Enhanced interhemispheric connectivity may counterbalance unilateral dysfunction. These compensatory processes rely on residual plasticity and network flexibility.

Maladaptive reorganization arises when compensation overshoots or stabilizes inefficient configurations. Excessive synchronization across broad regions reduces the capacity for differentiated processing. Persistent hyperconnectivity elevates background coupling, decreasing signal specificity. Overly segregated modules restrict integration, impairing complex cognitive functions. Rigid network states limit transitions between functional configurations required for adaptive behavior.

The distinction between compensation and maladaptation depends on dynamic stability. Networks capable of flexible reconfiguration maintain a wide repertoire of accessible states. Pathological networks often show reduced variability or unstable transitions. Increased susceptibility to sudden global shifts indicates loss of resilience. Network-level reorganization therefore reflects both structural adaptation and dynamical transformation.

Emergence of reorganization is not a linear extension of local dysfunction. It is the product of nonlinear amplification within interconnected systems. Recurrent loops magnify deviations in firing patterns. Hub vulnerability accelerates cascading effects. Activity-dependent plasticity consolidates new configurations. The final network phenotype represents an integrated outcome of these processes. Local synaptic perturbations thus evolve into distributed alterations that redefine the operational architecture of the brain.

5. Network Dynamics and Pathological Brain States

Network dynamics refer to the time-varying patterns of coordination that emerge from interactions among distributed neural populations. The brain does not operate as a static wiring diagram. It continually transitions between activity states shaped by oscillatory rhythms, coupling strength, and modulation from subcortical systems. These dynamic properties determine how information is integrated, segregated, and stabilized across large-scale systems. When synaptic and microcircuit disturbances accumulate, the dynamical regime of the network shifts. Pathological brain states can be understood as stable or recurrent patterns of activity that arise from altered network dynamics rather than from isolated structural defects.

Hypersynchrony represents one prominent pathological regime. In healthy networks, synchrony is spatially and temporally constrained. Oscillatory coupling allows distributed regions to coordinate during specific cognitive or motor demands, then decouple when tasks change. This flexible synchrony preserves both integration and differentiation. When excitation increases or inhibition weakens, synchrony may spread beyond functional boundaries. Hyperexcitable neuronal ensembles generate high amplitude oscillations that recruit neighboring circuits through existing structural connections. Local oscillatory bursts entrain distant regions, gradually increasing coherence across wider territories.

In epilepsy, such hypersynchrony evolves into seizure propagation. A focal region with enhanced excitatory transmission can generate rhythmic discharges that exceed inhibitory containment. These discharges synchronize adjacent networks through corticocortical and corticothalamic pathways. Thalamic circuits amplify rhythmic activity and redistribute it back to cortical areas, reinforcing the synchronous pattern. The seizure is not merely excessive firing. It is a large-scale transition into a globally coherent dynamical state characterized by reduced complexity and extreme phase alignment. Normal variability collapses into uniform oscillatory activity. The network becomes temporarily locked into a single attractor state dominated by hypersynchronous firing.

The propagation of seizures illustrates how structural connectivity shapes dynamic expression. White matter tracts determine the pathways through which pathological rhythms travel. Hub regions with dense connectivity accelerate spread by distributing synchronous input to multiple modules simultaneously. The

seizure state persists as long as excitatory drive and recurrent feedback maintain coherence. Termination often involves restoration of inhibitory dominance or metabolic exhaustion that disrupts synchronization.

In contrast to hypersynchrony, many neurodegenerative conditions display network slowing. Oscillatory power shifts toward lower frequency bands. Alpha rhythms may weaken, while theta and delta activity become more prominent. Slowing reflects reduced synaptic density and diminished efficacy of fast inhibitory circuits that normally support high frequency oscillations. Communication efficiency declines as conduction delays and synaptic failures accumulate. Phase relationships between regions lose precision, weakening long-range integration.

Network slowing is not simply reduced speed. It reflects a shift in the dynamical balance between excitation and inhibition and a decrease in the diversity of accessible states. Faster oscillations support fine temporal resolution and rapid information exchange. Slower rhythms integrate activity over longer windows but limit temporal specificity. When high frequency coordination declines, cognitive processes that depend on precise timing suffer. Memory consolidation, attentional selection, and motor coordination rely on coordinated rhythmic activity across distributed regions. As slowing progresses, networks exhibit reduced flexibility and diminished responsiveness to environmental demands.

Degeneration introduces structural constraints that reinforce dynamic slowing. Loss of hub integrity reduces global efficiency. Modules become more isolated. Signal propagation across distant regions requires more intermediate steps, increasing vulnerability to noise and temporal dispersion. Reduced connectivity compresses the network's dynamic range. Activity patterns become stereotyped and less adaptive.

Another defining feature of pathological networks is instability. Healthy brain dynamics fluctuate within bounded regimes that allow rapid transitions between states while maintaining overall stability. This balance reflects proximity to criticality, a condition in which the system can amplify relevant signals without becoming unstable. Synaptic perturbations shift this balance. Networks may move closer to bifurcation points where small inputs trigger disproportionate responses. Variability may increase as inhibitory control weakens, producing irregular bursts or oscillatory fragmentation.

Instability manifests as abrupt transitions between activity states. A system may alternate unpredictably between relative quiescence and excessive synchronization. In movement disorders, oscillatory activity may become locked into rigid beta rhythms that resist modulation. In cognitive disorders, networks may fail to transition efficiently between resting and task-engaged states. These impaired transitions reflect altered attractor landscapes in which certain states become overly stable while others become inaccessible.

State transitions in pathological networks often display nonlinear characteristics. Gradual synaptic changes accumulate until reaching a threshold. Beyond this point, the system reorganizes rapidly into a new dynamical configuration. Such transitions may correspond to clinical events such as seizure onset, sudden cognitive decline, or abrupt motor freezing. The underlying mechanism involves amplification through recurrent loops and hub-mediated integration. Once the network crosses a critical boundary, returning to the prior state becomes difficult.

Pathological brain states therefore represent emergent properties of altered network dynamics. Hypersynchrony compresses variability into excessive coherence. Slowing reduces temporal resolution and flexibility. Instability increases susceptibility to abrupt transitions. Each pattern reflects a distinct configuration of excitation, inhibition, connectivity strength, and oscillatory coordination. Synaptic pathology initiates these changes, microcircuit imbalance amplifies them, and large-scale networks express them as stable or recurrent dynamical regimes.

6. Cross-Disease Perspectives

A cross-disease perspective highlights recurring mechanistic patterns that link synaptic disturbance to large-scale network reorganization. Epilepsy, Alzheimer's disease, and Parkinson's disease differ in etiology, affected regions, and clinical presentation. Yet each condition demonstrates how localized synaptic alterations propagate through microcircuits and ultimately reshape distributed

brain systems. The direction of network change varies across disorders, but the hierarchical cascade from synapse to circuit to network remains a shared structural logic.

6.1 Epilepsy

Epilepsy exemplifies a condition in which increased synaptic excitation and reduced inhibitory control generate hypersynchronous network states. At the synaptic level, enhanced glutamatergic transmission may result from increased receptor density, altered subunit composition, or elevated presynaptic release probability. In parallel, impairment of inhibitory interneurons reduces gamma aminobutyric acid mediated regulation of pyramidal cell firing. The excitatory inhibitory equilibrium shifts toward heightened responsiveness.

Within local microcircuits, recurrent excitation becomes more dominant. Inhibitory timing precision declines, allowing pyramidal neurons to fire within overlapping temporal windows. Population spikes align more easily, increasing the probability of synchronous bursts. Oscillatory coordination changes as gamma rhythms lose fine structure and slower rhythms may become exaggerated. These microcircuit changes create conditions in which activity spreads beyond its normal spatial boundaries.

At the network level, hyperexcitable regions recruit connected areas through existing structural pathways. Thalamocortical loops amplify rhythmic discharge and redistribute it across cortical territories. Hub regions with dense connectivity accelerate propagation by synchronizing multiple modules simultaneously. The seizure represents a global dynamical transition characterized by extreme phase alignment and reduced complexity. Functional differentiation between regions collapses into uniform oscillatory activity. The pathological state is therefore not confined to a focal lesion but emerges as a network-wide configuration stabilized by recurrent synchronization.

Epilepsy demonstrates how increased synaptic gain and impaired inhibition translate into network hypersynchrony. The clinical expression reflects a distributed dynamical state rather than a purely local abnormality.

6.2 Alzheimer's Disease

Alzheimer's disease illustrates a contrasting trajectory marked by progressive synaptic degeneration and network fragmentation. Early in the disease course, synaptic dysfunction arises from disrupted receptor trafficking, impaired plasticity mechanisms, and interference with intracellular signaling pathways. Dendritic spine density decreases, and long term potentiation weakens. These changes precede extensive neuronal death.

Microcircuit consequences include diminished recurrent excitation and altered inhibitory modulation. Local ensembles exhibit reduced coherence, particularly in higher frequency bands associated with cognitive processing. The signal to noise ratio declines as weakened synaptic input fails to sustain stable firing patterns. Oscillatory activity shifts toward slower frequencies, reflecting diminished excitatory drive and impaired temporal precision.

At the network level, functional connectivity between associative cortical regions decreases. The default mode network, which supports episodic memory and integrative cognitive functions, shows reduced coupling and weakened hub integrity. Regions that once coordinated cross module communication lose centrality. Modules become more segregated. White matter degeneration further compromises long range synchronization by slowing conduction velocity and disrupting phase relationships.

The emergent network phenotype is characterized by disconnection and slowing rather than hypersynchrony. Cognitive deficits correlate more closely with synaptic density loss and network disintegration than with the magnitude of gross cortical atrophy. Alzheimer's disease thus exemplifies how progressive synaptic weakening leads to fragmentation of large scale systems and reduction of dynamic flexibility.

6.3 Parkinson's Disease

Parkinson's disease presents yet another pattern in which altered synaptic modulation reorganizes network rhythms without initial widespread synaptic loss. Dopaminergic depletion in the substantia nigra modifies synaptic efficacy within basal ganglia circuits. Dopamine normally regulates the balance between direct and indirect pathways controlling motor output. Its reduction shifts this balance, altering synaptic plasticity and neuronal firing patterns in the striatum and

related nuclei.

At the microcircuit level, abnormal synchronization emerges within the beta frequency range. Neuronal ensembles within the basal ganglia exhibit increased phase locking. Inhibitory and excitatory interactions become more rigid, reducing variability in firing patterns. This rigidity constrains the ability of circuits to transition between states necessary for fluid movement.

Large scale reorganization occurs through corticobasal ganglia loops. Excessive beta coherence propagates to motor cortex, entraining cortical neurons to subcortical rhythms. The motor network becomes dominated by persistent oscillatory coupling that resists modulation. Functional connectivity patterns shift toward overly stable synchronization, reducing flexibility required for initiating and adjusting movement. Rigidity and bradykinesia reflect this constrained network state rather than isolated neuronal loss.

Parkinson's disease demonstrates how altered neuromodulatory control at the synaptic level reshapes oscillatory dynamics and reorganizes motor networks. The pathological phenotype arises from rhythmic locking and reduced dynamical adaptability.

6.4 Comparative Synthesis

Across these disorders, distinct synaptic perturbations generate specific network signatures. Increased excitatory gain and impaired inhibition produce hypersynchronous global states in epilepsy. Progressive synaptic degeneration leads to fragmentation and slowing in Alzheimer's disease. Altered neuromodulatory balance induces rigid oscillatory coupling in Parkinson's disease. Each condition highlights a different direction of network reorganization, yet all share a hierarchical progression from synaptic disruption to system-level dynamical change.

Neurological diseases are not solely defined by anatomical location or molecular pathology. They are characterized by emergent network states that arise from accumulated synaptic alterations. Hypersynchrony, disconnection, slowing, and oscillatory rigidity represent distinct dynamical endpoints of the same multilevel cascade. Understanding these shared mechanisms clarifies why diverse etiologies converge on network dysfunction as the final common pathway of neurological disease.

7. A Multilevel Integrative Model

A multilevel integrative model provides a structured account of how microscopic alterations give rise to macroscopic pathological states. The central premise is that synaptic pathology does not remain confined to the molecular or cellular domain. It modifies the operating rules of neuronal interaction. These modified rules reshape local circuit computation. Local circuit reconfiguration alters patterns of large-scale communication. The final disease phenotype emerges from cumulative interactions across these nested levels.

Linking synaptic pathology to network phenotypes requires tracing changes in signal transformation step by step. At the synaptic level, alterations in receptor density, vesicle release probability, or postsynaptic responsiveness modify the input output function of neurons. A neuron that once responded selectively may become hyperresponsive or unresponsive. Its firing threshold, temporal precision, and adaptation profile shift. Because neurons are embedded within recurrent microcircuits, these altered response properties change how ensembles coordinate activity.

Microcircuits translate altered neuronal properties into collective dynamics. Inhibitory control may weaken or become excessively rigid. Oscillatory coordination may shift in frequency, amplitude, or coherence. The ensemble may favor synchronous bursts or fragmented asynchronous firing. These changes influence how information is routed to other regions. Long-range projections transmit patterns shaped by local imbalance. Target regions receive input that differs in timing and reliability from the previous baseline. Over time, reciprocal adjustments occur across connected nodes. Coupling strength adapts to new input statistics. Oscillatory alignment shifts. Network topology reorganizes.

The resulting network phenotype is not a simple sum of local deficits. It reflects the emergent configuration that arises when distributed nodes adapt to persistent alterations in effective connectivity. Some regions increase connectivity in response to weakened partners. Others disengage due to unreliable input. Hub nodes experience disproportionate strain because they integrate multiple altered streams. The final configuration may display hypersynchrony,

fragmentation, slowing, or instability depending on the direction of synaptic perturbation and the structure of the underlying connectome.

Threshold effects are central to this integrative model. Neural systems possess homeostatic mechanisms that buffer moderate perturbations. Synaptic scaling adjusts overall strength to maintain stable firing rates. Inhibitory circuits compensate for shifts in excitation. Network redundancy distributes computational load. These mechanisms allow early synaptic pathology to accumulate without immediate large-scale consequences. The system remains within a stable regime despite ongoing microscopic disruption.

As perturbations intensify, compensatory capacity diminishes. Critical parameters such as excitation inhibition balance, hub centrality, or oscillatory coherence approach boundary conditions. Once these parameters cross a threshold, qualitative transitions occur. A network that previously operated with flexible modular integration may abruptly fragment. A circuit that maintained stable oscillations may enter persistent hypersynchrony. These transitions reflect nonlinear dynamics inherent in recurrent systems. Small incremental changes in synaptic efficacy can lead to disproportionate shifts in global behavior when critical points are exceeded.

Nonlinear amplification emerges from feedback loops embedded at multiple levels. Recurrent excitation magnifies slight increases in synaptic gain. Hub vulnerability concentrates disruption within nodes that coordinate widespread communication. Activity dependent plasticity stabilizes emerging patterns by reinforcing frequently coactivated.

8. Implications for Therapeutic Strategies

A multilevel framework implies that therapeutic strategies should be aligned with the hierarchical organization of pathology. If synaptic disturbance initiates the cascade and network reorganization consolidates the disease phenotype, then mechanistic intervention can be conceptualized at several interconnected levels. The objective is not limited to suppressing symptoms. It involves restoring stability to communication parameters that govern neuronal interaction, circuit coordination, and large scale dynamics. Each level presents distinct leverage points that influence the overall trajectory of network reorganization.

8.1 Targeting Synaptic Stability

Synaptic stability forms the foundation of network integrity. Structural preservation of dendritic spines, maintenance of presynaptic release mechanisms, and stabilization of receptor distribution support reliable signal transmission. When synaptic architecture remains intact, neuronal response properties remain predictable. Mechanistic strategies at this level aim to preserve the molecular scaffolding that anchors synaptic proteins and regulates plasticity.

Equally important is the regulation of excitatory and inhibitory balance. Excess excitation increases gain and predisposes circuits to runaway synchronization. Excess inhibition suppresses adaptability and reduces information throughput. Mechanistic modulation of neurotransmitter systems seeks to recalibrate this balance so that firing thresholds return to a stable operating range. By restoring equilibrium at the synaptic interface, downstream microcircuit instability may be reduced.

Plasticity mechanisms also represent a central target. Long term potentiation and long term depression shape memory encoding and network adaptation. If potentiation becomes excessive, pathological circuits may stabilize. If depression dominates, functional disconnection may progress. Supporting regulated plasticity preserves flexibility while preventing maladaptive consolidation. The aim is to maintain a dynamic equilibrium in which synapses remain responsive without becoming destabilized.

Synaptic level intervention addresses the origin of pathological cascades. Stabilizing communication at this foundational layer reduces the likelihood that microcircuit imbalance will propagate outward. Because synapses represent the entry point of disruption, maintaining their structural and functional integrity may alter disease progression before large scale reorganization becomes entrenched.

8.2 Modulating Network Oscillations

Large scale networks coordinate activity through oscillatory synchronization. Rhythms in specific frequency bands structure temporal windows for information exchange. Pathological conditions often exhibit exaggerated synchrony, rigid oscillatory locking, or slowing of rhythmic activity. Modulating these oscillations directly influences how distributed regions interact.

Adjusting oscillatory amplitude and phase relationships can recalibrate network coordination. When hypersynchrony dominates, reducing excessive coherence may restore differentiation between modules. When slowing and fragmentation prevail, enhancing appropriate rhythmic coupling may strengthen integration. Oscillatory modulation changes the dynamical regime of the system without necessarily altering underlying structural connectivity.

Mechanistic approaches that influence rhythmic coordination act on temporal organization rather than on static wiring. They aim to reshape attractor landscapes within which network states evolve. By adjusting oscillatory parameters, it becomes possible to shift the network away from pathological states and toward more flexible configurations. The focus lies on restoring the balance between integration and segregation that supports adaptive cognition and motor control.

Oscillatory modulation also influences plasticity. Rhythmic synchronization determines which synapses strengthen through timing dependent mechanisms. By recalibrating oscillatory patterns, it is possible to indirectly influence synaptic reinforcement and weaken maladaptive loops. This demonstrates how intervention at the network level can feed back to earlier stages of the cascade.

8.3 Early Intervention at the Microcircuit Level

Microcircuits represent a critical amplification stage in the progression from synaptic pathology to network reorganization. Intervening at this intermediate level may prevent nonlinear escalation. Stabilizing interneuron function preserves inhibitory precision and maintains temporal structure within local ensembles. When inhibitory timing remains intact, excitatory bursts are contained and synchronization remains spatially constrained.

Preserving signal to noise ratio within microcircuits protects the fidelity of information transmitted to distant regions. When noise increases, downstream networks must adapt to unreliable input, accelerating reorganization. Maintaining microcircuit precision reduces the burden placed on large scale systems. This limits compensatory overconnectivity and prevents fragmentation.

Early microcircuit intervention also aims to preserve oscillatory coordination within local networks. If gamma or beta rhythms destabilize at an early stage, restoring their coherence may prevent propagation of abnormal timing to long range connections. Because oscillatory disturbances bridge the gap between local and global dysfunction, stabilizing rhythms at the microcircuit level interrupts the cascade before network phenotypes consolidate.

Timing of intervention is central in this framework. Once large scale reorganization stabilizes through repeated plastic reinforcement, reversing it becomes increasingly difficult. Early correction of microcircuit imbalance may maintain the system within a resilient regime where compensatory mechanisms remain adaptive rather than maladaptive. The goal is to prevent threshold crossing that leads to abrupt dynamical transitions.

9. Conclusion

Synaptic pathology is not an isolated microscopic event. It represents the initiating disturbance within a hierarchically organized system whose stability depends on tightly coordinated interactions across scales. A single synapse embodies molecular signaling, structural scaffolding, and dynamic plasticity. When these properties are altered, the impact does not remain confined to the point of contact between two neurons. The alteration modifies neuronal responsiveness, reshapes microcircuit timing, and ultimately influences distributed communication patterns. Through microcircuit imbalance and oscillatory disruption, synaptic changes extend outward into large scale network reorganization. Network remodeling emerges as the defining systems level expression of many neurological diseases.

The trajectory from synaptic perturbation to network phenotype reveals that neurological disorders are fundamentally disorders of interaction. The brain's architecture is constructed upon nested feedback loops in which local and global processes continuously influence one another. Synaptic dysfunction shifts the parameters governing excitation, inhibition, and plasticity. Microcircuits translate these shifts into altered ensemble coordination. Large scale networks adapt to persistent changes in effective connectivity. Over time, new dynamical states stabilize. These states may manifest as hypersynchrony, fragmentation,

slowing, or oscillatory rigidity depending on the direction and distribution of the initial perturbation.

Understanding disease in this way challenges strictly localization based interpretations. Visible lesions or regional atrophy represent late stage markers within a broader cascade. Clinical symptoms frequently correspond more closely to network level configuration than to the magnitude of structural damage. Cognitive decline, seizure propagation, or motor rigidity arise from reorganized communication patterns that reflect accumulated synaptic disturbance. The system behaves differently because the rules of interaction have shifted.

A multilevel perspective integrates structural and functional viewpoints into a coherent framework. Structural synaptic alterations change the physical substrate of connectivity. Functional microcircuit imbalance modifies timing and gain control. Network dynamics reorganize according to these altered inputs. Feedback between levels consolidates the new configuration. This integrative view explains why small molecular abnormalities can generate disproportionate behavioral consequences and why diverse diseases converge on characteristic network signatures.

The brain's resilience lies in its capacity for compensation and plastic adaptation. Early synaptic disruption may be buffered by homeostatic mechanisms. Microcircuits may adjust inhibitory thresholds. Networks may recruit alternative pathways. Disease progression reflects the gradual exhaustion or maladaptation of these compensatory processes. When critical thresholds are crossed, qualitative shifts in network state occur. At that point, the pathological configuration becomes self reinforcing through recurrent synchronization or persistent disconnection.

Conceptualizing neurological disease as a dynamic cascade emphasizes continuity rather than fragmentation. Synaptic pathology initiates deviation from equilibrium. Microcircuit reorganization amplifies deviation. Network reconfiguration expresses deviation as a stable or recurrent brain state. Each level is necessary to understand the full phenotype. Ignoring any layer produces an incomplete explanation.

A comprehensive account of neurological disorders therefore requires tracing interactions across hierarchical scales. Synapses encode the rules of communication. Microcircuits implement those rules in collective activity. Networks embody the global architecture shaped by ongoing interaction. Pathology unfolds when these elements lose coordinated balance. By recognizing the multilevel nature of this process, the complexity of pathological brain states becomes intelligible as the emergent outcome of interconnected disturbances rather than as isolated structural defects.

References

Bassett, D. S., & Sporns, O. (2017). Network neuroscience. *Nature Neuroscience, 20*(3), 353–364. https://doi.org/10.1038/nn.4502

Ben-Ari, Y. (2008). Ben-Ari Y. (2014). The GABA excitatory/inhibitory developmental sequence: a personal journey. *Neuroscience*, *279*, 187–219. https://doi.org/10.1016/j.neuroscience.2014.08.001

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science (New York, N.Y.)*, *304*(5679), 1926–1929. https://doi.org/10.1126/science.1099745

Buzsáki, G., & Wang, X.-J. (2012). Mechanisms of gamma oscillations. *Annual Review of Neuroscience, 35*, 203–225. https://doi.org/10.1146/annurev-neuro-062111-150444

de Haan, W., Mott, K., van Straaten, E. C. W., Scheltens, P., & Stam, C. J. (2012). Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. *PLoS Computational Biology, 8*(8), e1002582. https://doi.org/10.1371/journal.pcbi.1002582

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences, 9*(10), 474–480. https://doi.org/10.1016/j.tics.2005.08.011

Levy, R., & Goldman-Rakic, P. S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain Research, 133*(1), 23–32. https://doi.org/10.1007/s002210000397

Palop, J. J., & Mucke, L. (2010). Amyloid-β–induced neuronal dysfunction in Alzheimer's disease: From synapses toward neural networks. *Nature Neuroscience, 13*(7), 812–818. https://doi.org/10.1038/nn.2583

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage, 52*(3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003

Stam, C. J. (2014). Modern network science of neurological disorders. *Nature Reviews Neuroscience, 15*(10), 683–695. https://doi.org/10.1038/nrn3801

Turrigiano, G. G. (2012). Homeostatic synaptic plasticity: Local and global mechanisms for stabilizing neuronal function. *Cold Spring Harbor Perspectives in Biology, 4*(1), a005736. https://doi.org/10.1101/cshperspect.a005736

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: Relevance for cognitive dysfunctions and pathophysiology. *Neuron, 52*(1), 155–168. https://doi.org/10.1016/j.neuron.2006.09.020

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nature Reviews Neuroscience, 11*(2), 100–113. https://doi.org/10.1038/nrn2774

Varela, F., Lachaux, J.-P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: Phase synchronization and large-scale integration. *Nature Reviews Neuroscience, 2*(4), 229–239. https://doi.org/10.1038/35067550

Wang, X.-J. (2010). Neurophysiological and computational principles of cortical rhythms in cognition. *Physiological Reviews, 90*(3), 1195–1268. https://doi.org/10.1152/physrev.00035.2008

Current Research in Medical Sciences
ISSN 2958-0390
www.paradigmpress.org/crms
Volume 5 Number 1 January 2026

Institutional Mechanisms Shaping the Digital Divide Among Older Patients in China's Appointment-Based Outpatient System

Wenjie Huang[1] & Liang Chen[1]

[1] Anhui Medical University, China
Correspondence: Liang Chen, Anhui Medical University, China.

doi:10.63593/CRMS.2026.01.05

Abstract

Digital appointment systems have become the primary entry mechanism for outpatient care in China's public hospitals. At the same time, rapid population aging has increased the proportion of older adults within the healthcare system. Although digital access among older adults has expanded, disparities remain in their ability to navigate complex procedural platforms. Existing discussions often interpret this situation as a problem of individual digital literacy. This paper adopts a different perspective and examines the digital divide as an institutional outcome.

Through a structural analysis of policy rationality, organizational restructuring, and micro-level interaction processes, the study shows how digital competence becomes embedded as an implicit entry condition. Platform-centered allocation mechanisms link procedural performance to resource access, especially in high-demand specialist services. Repeated differences in appointment acquisition gradually translate into disparities in medical quality and health trajectories. Over time, these patterns stabilize and become normalized within routine hospital governance.

The findings suggest that the digital divide in outpatient care is not merely a technological gap but a structured consequence of institutional design. Rebalancing efficiency and equity in aging societies requires adjustments in access pathways rather than sole reliance on individual adaptation.

Keywords: digital divide, appointment-based outpatient system, aging population, institutional design, healthcare governance, platformization, access inequality

1. Introduction

In the past ten years, outpatient care in China has changed significantly because of digital reform. Appointment-based systems are no longer optional. They have become the main way to enter hospital services in many cities. Large tertiary hospitals require patients to book visits through mobile applications, hospital websites, or public service platforms. The *Statistical Communiqué on the Development of Health and Medical Services in China* issued by the National Health Commission shows that almost all tertiary public hospitals now provide appointment services. In many major cities, more than 70 percent of outpatient visits in leading hospitals are booked online. What began

as a measure to reduce long queues has gradually become a routine institutional arrangement in hospital management.

At the same time, China is experiencing rapid population aging. Data from the Seventh National Population Census indicate that by the end of 2020, the population aged 60 and above had reached 264 million, accounting for 18.7 percent of the total population. The proportion has continued to increase in subsequent years. Digital technology has also expanded across society. The China Internet Network Information Center reports that internet use among older adults has grown steadily. However, differences remain in usage depth and operational ability. Many older adults use smartphones for basic communication and simple applications. Tasks that involve multiple steps, such as online registration, real-name verification, and time-slot selection, remain challenging for a considerable portion of this group.

Key demographic and digital indicators are summarized below.

Table 1. Aging Population and Digital Usage Among Older Adults in China

Indicator	Year	Value	Source
Population aged 60+	2020	264 million (18.7%)	Seventh National Population Census
Population aged 65+	2020	190.6 million (13.5%)	Seventh National Population Census
Internet users aged 60+	2022	Approx. 153 million	CNNIC Statistical Report
Internet penetration rate (60+)	2022	Around 52%	CNNIC Statistical Report

These figures show two structural trends. The older population is large and growing. Internet access among older adults has increased. Digital inclusion in basic terms is expanding. At the same time, digital participation does not necessarily mean digital competence in complex institutional procedures.

Digital medical reform and population aging now intersect within the same institutional space. The appointment system assumes that patients can use digital tools independently. Many older patients cannot do this easily. In the past, access to outpatient services depended on physical presence. Patients waited in line. The system was slow but visible. The current model replaces physical waiting with procedural navigation on digital platforms. Access now depends on successful digital operation.

Public discussion often explains this situation as a digital divide caused by lack of skills among older adults. The focus remains on individual adaptation. Proposed solutions include digital training programs, family assistance, and simplified interface design. These responses address surface difficulties. They do not explain why access disparities persist even as smartphone ownership expands. They also do not explain how small differences in digital ability can produce large differences in access to scarce medical resources.

This paper approaches the issue from a different angle. It does not treat the digital divide as a problem of personal deficiency. It treats it as a consequence of institutional design. The shift toward digital appointments reflects a governance logic that prioritizes efficiency, traceability, and resource control. Embedded within this logic are assumptions about what patients can do and how they should behave. When these assumptions encounter an aging population with uneven digital competence, structural mismatches emerge. The central question is not why some older patients lack digital skills. The central question is how institutional arrangements convert differences in digital ability into unequal access to healthcare.

2. Reframing the Digital Divide as an Institutional Outcome

The concept of the digital divide has been widely discussed in studies of technology and society. Early research focused on access to devices and internet connections. Later studies examined differences in skills, frequency of use, and types of online activity. In many cases, the divide is explained as a gap between those who can use digital tools effectively and those who cannot. The emphasis stays on individual capacity. Older adults are often described as a vulnerable group because they are less familiar with new technologies and less confident in using complex digital systems.

This line of explanation is useful in showing

unequal patterns of digital participation. It does not fully capture what happens in the field of healthcare. In medical settings, digitalization is not simply a matter of adopting new tools. It is a process of institutional restructuring. When hospitals introduce appointment platforms, online registration systems, and real-name verification procedures, they are not just offering additional options. They are redesigning the rules of access. Digital procedures become embedded in formal workflows. They define how patients enter the system, how resources are distributed, and how time is allocated.

Under these conditions, digital technology operates as part of an institutional framework. It shapes expectations about patient behavior. It sets procedural requirements that must be completed before care can be received. The system assumes that patients are able to navigate interfaces, follow multi-step instructions, and respond to automated prompts. These assumptions are often invisible because they are built into the structure of the system itself. Patients who meet these expectations pass through the process smoothly. Patients who do not meet them face delays, confusion, or exclusion.

The key issue, therefore, is not only whether older adults possess digital skills. The more important issue is how institutional arrangements convert differences in ability into differences in access. When digital competence becomes a condition for obtaining medical appointments, capability differences turn into structural barriers. The digital divide is no longer a simple gap in technology use. It becomes a product of institutional design. It emerges from the mismatch between the assumptions embedded in digital reform and the actual capability structure of an aging population.

This perspective shifts the focus of analysis. Instead of asking how older adults can adapt to digital systems, the analysis asks how digital systems define acceptable forms of participation. It examines how policy rationality, organizational restructuring, and procedural requirements shape patterns of inclusion and exclusion. The following sections develop this analytical framework by examining the governance logic behind digital reform, the reorganization of outpatient access, and the micro-level processes through which exclusion is produced.

3. Policy Rationality and the Hidden Assumptions of Digital Reform

3.1 Efficiency-Centered Governance Logic

The expansion of appointment-based outpatient systems in China did not take place by chance. It emerged within a broader reform agenda that seeks to improve efficiency in public service delivery. Large public hospitals face high patient volumes, limited specialist resources, and strong public demand. Long queues, overnight waiting, and crowd congestion were common problems in major cities. Digital appointment systems were introduced as a way to manage these pressures.

Official policy documents from the National Health Commission have repeatedly emphasized orderly medical treatment, time-based appointments, and information-based management. The stated goals include reducing on-site congestion, improving resource allocation, and strengthening traceability of medical services. Online booking makes it possible to distribute patient flow across time slots. It also allows hospitals to monitor demand patterns and adjust schedules. In this governance framework, efficiency is closely linked to control and predictability.

Digital platforms support this model by standardizing procedures. Each patient must complete a fixed sequence of steps before obtaining an appointment. The system records identity information, department selection, time slot choice, and payment status. These processes create data that can be tracked and analyzed. Hospital managers can use these data to evaluate workload distribution and reduce idle capacity. The digital interface becomes part of the management toolset.

This efficiency-centered logic prioritizes smooth workflow and measurable outcomes. Physical queuing is seen as disorderly and hard to regulate. Digital queuing, in contrast, can be structured and monitored. The shift from on-site registration to online booking is therefore not only a technical adjustment. It reflects a preference for rule-based, standardized, and data-driven governance. Within this framework, the main concern is whether the system operates smoothly. Less attention is given to how different patient groups experience the new entry requirements.

When efficiency becomes the dominant policy value, access is reorganized around procedural compliance. Patients who can follow the digital process benefit from faster and more predictable service. Patients who struggle with the process face additional barriers before reaching clinical care. The governance logic does not explicitly aim to exclude older adults. It does, however, define access in a way that assumes procedural competence. This assumption forms the background against which digital exclusion begins to take shape.

3.2 Implicit Presumption of Universal Digital Competence

The efficiency-centered reform described above rests on a silent premise. The system assumes that patients are able to complete the digital process on their own. This assumption is rarely stated in policy documents. It is embedded in the design of the platform and in the sequence of required steps. To obtain an appointment, a patient must download an application or access a website, register an account, complete real-name verification, select a department, choose a time slot, confirm payment, and receive electronic confirmation. Each step requires a certain level of familiarity with smartphones and online procedures.

The system treats these actions as routine. It does not distinguish between patients with different levels of digital literacy. There is no built-in screening of digital capacity. Instead, the ability to navigate the interface becomes an informal prerequisite for access. The platform is designed for independent operation. It does not assume that users will need continuous assistance. In this sense, digital competence is treated as a universal condition.

This implicit presumption shapes the entry conditions of the outpatient system. In the past, access depended mainly on physical presence. A patient could go to the hospital, wait in line, and speak directly to registration staff. The main requirement was time and mobility. Under the digital model, the requirement shifts to procedural ability. Patients must demonstrate competence before they can even enter the waiting system. Those who cannot complete the steps are filtered out before reaching clinical care.

The filtering effect does not operate through explicit exclusion. There is no rule that prohibits older adults from making appointments. The exclusion occurs through procedural design. When the interface is complex, when verification codes must be entered quickly, when time slots are released at fixed moments, the system favors users who are familiar with digital routines. Small differences in skill lead to large differences in outcome. A missed time window or an incorrect input can mean losing access to a specialist slot.

The assumption of universal digital competence therefore functions as a hidden institutional threshold. It defines who can pass smoothly through the system and who cannot. The requirement is not visible as a formal policy condition. It appears neutral and technical. In practice, it reorganizes the boundary of participation. Digital competence becomes the new form of eligibility. This is how institutional assumptions shape entry conditions and transform capability differences into structured barriers.

4. Organizational Restructuring and the Relocation of Access Gateways

4.1 Transformation of the Entry Point

The shift to appointment-based outpatient care has changed where and how patients enter the hospital system. In the past, the main entry point was physical space. Patients went to the hospital early in the morning. They waited in line at the registration window. Access depended on arrival time, physical presence, and patience. The hospital gate and the registration hall were the first barriers. The order of service was visible and based on spatial sequence.

Under the digital appointment system, this entry point has moved. The first barrier is no longer the hospital building. It is the digital platform. Patients must secure a time slot before they arrive. Without a confirmed appointment, access to many departments is limited or not allowed. The process of entry now begins on a smartphone screen. The platform becomes the new gate.

This transformation changes the logic of access. Physical queuing follows a spatial logic. Patients compete through presence. Digital booking follows a platform logic. Patients compete through speed of operation and familiarity with the interface. When appointment slots are released at fixed times, users must log in, select departments, and confirm quickly. Those who can navigate the system fast have an advantage.

Those who hesitate or make mistakes may lose the opportunity.

The relocation of the entry point also changes visibility. In physical queues, patients can see their position. They can observe how the line moves. In digital systems, the process is less transparent. Appointment slots may disappear within seconds. The competition happens on screens that are not shared. This reduces the sense of collective waiting and replaces it with individualized interaction.

The new entry structure reshapes the relationship between patients and institutions. Hospitals no longer manage crowds only in physical space. They manage demand through digital filters. The platform decides who enters the next stage of care. This organizational shift places digital competence at the very beginning of the treatment process. Access to medical resources starts with successful interaction with the system rather than with arrival at the hospital.

4.2 Platformization and Resource Allocation

As the entry point moves to digital platforms, the platform becomes the center of resource allocation. It is no longer only a booking tool. It becomes the mechanism through which outpatient resources are distributed. Specialist clinics, popular departments, and limited expert slots are released and managed through the system. The platform controls the timing, quantity, and visibility of available appointments.

National statistics and policy reports indicate the extent of this transformation. Appointment-based management is now standard practice in tertiary public hospitals. In many major urban hospitals, online booking accounts for the majority of outpatient registrations. The platform has therefore shifted from an auxiliary channel to the dominant allocation mechanism.

Table 2. Digital Appointment Coverage in Public Hospitals in China

Indicator	Approximate Level	Source
Tertiary public hospitals providing appointment services	Nearly 100% coverage	National Health Commission Statistical Communiqué
Major urban tertiary hospitals with online booking systems	Universal implementation	National Health Commission
Online booking proportion in leading urban hospitals	Often above 70% of outpatient visits	Hospital annual reports / municipal health data

These figures show that digital platforms are not marginal tools. They form the structural core of outpatient entry in large public hospitals. When the majority of appointments are distributed online, the platform defines how medical resources circulate.

In many hospitals, expert appointments are released at fixed times. Patients must log in at that moment and compete for limited slots. This practice is often described as “online grabbing.” The speed of operation, network stability, and familiarity with the interface influence the outcome. The platform determines how long a slot is reserved before payment. It determines how many attempts are allowed. These technical rules structure competition.

Under this arrangement, digital performance becomes directly connected to resource access. Patients who understand release schedules and can operate quickly increase their chances of securing high-demand appointments. Patients who are unfamiliar with these patterns often miss opportunities. They may not know when slots are released. They may not complete the process within the required time. Access to scarce medical resources therefore becomes linked to digital competence.

The platform also centralizes and standardizes information. Departments, doctors, schedules, and fees are displayed in fixed formats. This supports administrative control and data management. It limits flexibility at the same time. In earlier registration systems, patients could interact with staff and request clarification. In the platform model, the interface defines the range of choices. What appears on the screen becomes the boundary of possibility.

Through platformization, outpatient resources

are no longer allocated mainly through physical presence. They are allocated through procedural completion and digital interaction. The system applies uniform rules. These rules appear neutral. Their effects are not uniform. When high-value appointments depend on rapid and accurate digital action, users with stronger digital skills gain structural advantages. The platform thus functions as both allocator and filter within the outpatient system.

4.3 Contraction of Offline Alternatives

The growth of digital appointment systems has also changed the role of offline registration channels. In many large hospitals, the number of on-site registration windows has been reduced. Some hospitals reserve only a small portion of slots for walk-in patients. In certain departments, appointments must be made online in advance. Patients without a confirmed booking may be asked to use self-service machines or mobile platforms inside the hospital.

This reduction of offline options weakens the fallback mechanisms that once balanced differences in ability. In the past, patients who were unfamiliar with new procedures could rely on staff at registration counters. Face-to-face communication allowed clarification and correction. Staff could guide patients through department selection and scheduling. This human support acted as a buffer. It reduced the impact of skill differences.

Under the platform-centered model, that buffer becomes thinner. Self-service kiosks often mirror the same digital steps found in mobile applications. They require identity verification and time-slot selection through touch screens. If assistance desks exist, they may focus on technical guidance rather than full substitution. The responsibility shifts to the patient to complete the digital process. Offline space no longer guarantees equal entry.

Organizational restructuring therefore changes how capability differences translate into outcomes. When offline channels shrink, patients with limited digital skills lose compensatory pathways. Patients with stronger digital competence are able to secure appointments in advance. They arrive at the hospital with confirmed slots. Patients who depend on offline registration face uncertainty. They may find that no slots remain. In this way, digital ability turns into a practical advantage in accessing scarce resources.

The system does not openly rank patients by skill. It maintains uniform procedures. However, by narrowing offline alternatives, the organization reduces its capacity to offset inequality in digital competence. Digital ability becomes directly linked to resource acquisition. The weakening of compensatory channels is therefore a key step in the conversion of technological difference into structured advantage.

5. Micro-Level Production of Digital Exclusion

5.1 Cognitive and Interface Complexity

Digital exclusion is not produced only at the level of policy or organization. It is also produced through everyday interaction with the appointment system. The structure of the interface and the sequence of required steps play a direct role in shaping access. What appears to be a neutral technical process often contains multiple layers of procedural demand.

Most hospital appointment platforms require users to complete several consecutive steps. A patient must log in, select a hospital, choose a department, identify a specific doctor, review available time slots, confirm personal information, complete real-name verification, and finalize payment. Each step requires attention and accuracy. Missing one step means starting again. For users familiar with digital systems, these actions feel routine. For many older adults, they create cognitive pressure.

Verification mechanisms add another layer of difficulty. Many platforms require users to enter short-lived verification codes sent by text message. These codes must be read, remembered, and entered quickly. The time limit is often strict. If the code expires, the process must be repeated. This design assumes that users can switch between applications, copy information correctly, and respond within seconds. For individuals with slower reaction time or limited experience with smartphone navigation, this requirement becomes a barrier.

Real-name binding also introduces procedural complexity. Patients must input identification numbers, confirm personal details, and sometimes upload documents. Errors in typing can lead to system rejection. Correction procedures are not always clear. The process demands a level of familiarity with digital forms and standardized input rules. Even small

mistakes can prevent completion.

Time-slot selection further intensifies the filtering effect. Many specialist appointments are released in limited quantities at fixed times. Users must understand release schedules and act quickly. The interface may refresh automatically, and available slots can disappear within moments. Successful booking depends on both speed and confidence in navigating options. Hesitation increases the chance of failure.

These layers of complexity do not operate as explicit exclusion rules. They function as procedural filters. The system does not ask whether a user is digitally skilled. It simply requires successful completion of each step. Users who can manage the sequence pass through. Users who struggle drop out at different stages. The cumulative effect of multi-step navigation, verification demands, and time pressure transforms small capability differences into decisive outcomes.

In this way, institutional design shapes access through interactional detail. The interface becomes a site where governance logic meets individual capacity. The complexity of the process is not accidental. It reflects priorities such as security, accuracy, and control. Yet these priorities also create a layered screening mechanism. Digital competence becomes the condition for entry, and the appointment system quietly sorts users according to their ability to handle procedural complexity.

5.2 Delegated Access and Loss of Autonomy

When older patients cannot complete digital procedures on their own, they often turn to others for help. This leads to delegated access. The act of booking an appointment shifts from the patient to another person. Access to care becomes dependent on social networks rather than individual action.

One common form is assistance from adult children. Many older patients ask their sons or daughters to register accounts, monitor release times, and secure appointments. This arrangement may work in families with available and digitally skilled members. It does not work equally for all households. Some older adults live alone. Some have children who work long hours or live far away. Access then depends on the availability and willingness of family members. Medical appointments become coordinated around family schedules instead of patient needs.

A second form is reliance on third-party intermediaries. Some patients pay service providers to complete the booking process. These intermediaries monitor appointment release times and use multiple devices to increase success rates. In high-demand departments, this practice has become common. It introduces additional costs. Patients with financial resources can improve their chances. Patients without such resources remain at a disadvantage.

There is also the reappearance of informal brokers often described as “scalpers.” Although digital platforms were partly introduced to reduce in-person scalping, the logic of scarcity remains. When expert slots are limited and highly competitive, new forms of brokerage emerge in online space. Individuals with strong digital skills can secure appointments and resell them. The platform does not directly endorse this behavior, but the structure of competition makes it possible.

These patterns show that limited digital ability does not simply block access. It creates dependency. Older patients who cannot navigate the system must rely on family, market actors, or informal networks. This dependence changes the meaning of autonomy in healthcare. The ability to seek medical treatment becomes mediated by others. Decision-making and timing are no longer fully under the patient’s control.

Delegated access also reshapes inequality. Patients with strong family support or financial means can compensate for digital limitations. Patients without such support face repeated failure or delayed care. Capability gaps therefore expand into social and economic differences. The appointment system does not directly require delegation. It produces conditions in which delegation becomes necessary for some groups. In this way, digital exclusion at the micro level leads to structured patterns of dependence within the healthcare system.

5.3 Psychological Withdrawal and Institutional Alienation

Digital exclusion does not stop at procedural difficulty. It gradually enters the psychological domain. When older patients encounter repeated obstacles in the appointment process, their response is not limited to technical

frustration. Emotional reactions begin to shape behavior. The interface may appear simple to experienced users, yet for many older adults it feels unstable and fast-moving. Pages refresh quickly. Appointment slots disappear within seconds. Error messages interrupt the process. Each failed attempt increases tension.

The structure of online booking introduces a new type of uncertainty. In physical queues, waiting is visible. Patients can see how many people are ahead of them. They can estimate time through observation. The digital platform removes this spatial transparency. The competition takes place in an invisible environment. Users cannot observe others. They cannot assess their position in line. When a desired slot disappears, there is no visible explanation. The experience creates a sense of unpredictability. For older patients who are accustomed to tangible procedures, this invisibility weakens their sense of control.

Anxiety grows when success depends on speed and accuracy. Verification codes must be entered within limited seconds. Time slots must be selected quickly. Any hesitation may lead to failure. For users who type slowly or who need time to read instructions carefully, this structure produces pressure. The body reacts to the countdown timer and rapid screen changes. What appears to be a neutral interface becomes a source of cognitive stress.

Repeated failure affects self-perception. When older patients cannot secure appointments despite multiple attempts, they may attribute failure to personal inadequacy. They may believe that they are “not capable” or “too old to understand.” This internalization of failure has consequences. Confidence in interacting with digital systems decreases. A single unsuccessful experience does not produce withdrawal. Continuous unsuccessful experiences create a pattern. That pattern reshapes expectations.

Behavioral withdrawal often follows psychological strain. Some older patients stop trying to book appointments online. They postpone visits. They wait until symptoms worsen. They avoid departments that require online reservation. In chronic disease management, delayed consultation interrupts continuity of care. The system does not formally deny access. The withdrawal occurs at the level of patient decision. The exclusion is silent.

This withdrawal also alters the patient’s relationship with the institution. Hospitals appear procedural rather than relational. The interaction shifts from speaking with staff to interacting with screens. Older adults who value face-to-face communication may feel detached from the system. They do not experience the hospital as a responsive organization. They experience it as a rigid platform.

Trust can erode under these conditions. When access depends on digital speed instead of perceived medical need, fairness becomes questionable in the eyes of some patients. They may believe that those who are more skilled with phones gain advantage. The impression of competition replaces the expectation of equal treatment. Even if the rules are uniform, the outcomes are uneven. This perception weakens institutional legitimacy at the individual level.

Dependence on others intensifies the sense of alienation. When patients must rely on children or third parties to secure appointments, autonomy declines. The act of seeking medical care becomes mediated. Older adults may feel hesitant to ask for help repeatedly. They may worry about burdening family members. This emotional hesitation contributes to delayed action. The system thus shapes not only access but also family dynamics.

Institutional alienation does not mean open resistance. It appears as distance. Patients comply when assistance is available. They withdraw when it is not. The hospital remains physically present, yet psychologically distant. Interaction becomes transactional rather than communicative. For patients who built expectations of care in an earlier administrative model, this transformation alters the meaning of medical access.

Over time, psychological withdrawal reinforces structural inequality. Patients who continue to engage with the digital system secure timely appointments. Patients who retreat lose opportunities. The gap widens not through explicit policy discrimination but through cumulative behavioral differences. The digital interface becomes the site where governance logic meets human vulnerability.

This process reveals that exclusion is not only technical. It is relational and emotional. The appointment platform filters users through procedural requirements. It also reshapes how patients understand their position within the healthcare system. When digital interaction

repeatedly produces stress, confusion, or failure, the result is not only missed appointments. It is reduced willingness to participate.

In an aging society, this psychological dimension carries long-term implications. Older adults form a growing share of outpatient users. If a portion of this group disengages from digital systems, the gap between institutional design and population needs widens. The system continues to operate efficiently for those who adapt. It becomes increasingly distant for those who do not. Exclusion thus stabilizes through everyday experience.

The micro-level production of digital exclusion therefore involves more than interface complexity and delegated access. It includes a gradual shift in perception. Older patients move from active participants to hesitant users. Some become passive observers of a system that feels difficult to navigate. The withdrawal is quiet. It leaves few visible traces in administrative data. Yet its impact accumulates across time.

Digital reform was designed to reduce congestion and improve order. It succeeds in organizing patient flow. At the same time, it reorganizes emotional engagement. The platform does not intend to produce alienation. The outcome emerges from repeated interaction between standardized procedures and uneven capabilities. Psychological withdrawal becomes the final stage in the conversion of digital difference into institutional distance.

This is why digital exclusion must be understood as more than a technical gap. It is a process through which institutional structure shapes behavior, emotion, and trust. The appointment system does not openly reject older patients. It creates conditions under which some of them step back. The step back is voluntary in form. It is structured in origin.

6. Institutionalization of the Digital Divide

The previous sections have traced how digital reform reshapes entry conditions, reorganizes allocation rules, and filters users through procedural requirements. The process can be summarized as a sequence of institutional transformation.

Table 3. Mechanism of Institutionalization of the Digital Divide

Stage	Institutional Process	Structural Effect
1	Digital competence embedded as entry condition	Capability filtering
2	Repeated differential appointment access	Resource stratification
3	Stabilized allocation patterns	Structured inequality

This sequence shows how digital competence becomes gradually embedded in the structure of access. When digital interaction becomes the primary condition for outpatient entry, differences in ability begin to translate into differences in resource acquisition. The change does not occur at a single moment. It develops through repeated encounters with the platform. Patients who navigate the system efficiently secure appointments earlier, select preferred time slots, and reach high-demand specialists. Patients who struggle face delays, missed opportunities, or repeated failure. Over time, digital competence becomes closely tied to the ability to obtain scarce medical resources.

As these patterns repeat, access differences extend beyond scheduling. In large public hospitals, specialist consultations and key departments often have limited daily quotas. When these quotas are distributed through digital release mechanisms, timing and speed shape outcomes. Patients who monitor release schedules and respond quickly increase their success rate. Patients who hesitate or depend on assistance are less likely to secure appointments. The rule remains formally equal. The outcomes become uneven.

Accumulated differences influence clinical pathways. Timely access to specialists supports early diagnosis and structured treatment planning. Delayed access may allow conditions to worsen before intervention. In chronic disease management, regular follow-up enables medication adjustment and monitoring. Interrupted follow-up weakens continuity of care. The gap in digital competence therefore shifts from procedural difference to difference in clinical trajectory.

Once access patterns stabilize, medical quality differences emerge. Patients who regularly obtain specialist care benefit from more detailed evaluation and tailored treatment. Patients who encounter repeated barriers may rely on

lower-level facilities or postpone care. The difference is not the result of explicit discrimination. It develops through institutional mediation. Digital systems define who can enter higher tiers of service smoothly and who cannot.

Health outcomes reflect these layered processes. Delayed diagnosis, irregular consultation, and fragmented treatment may influence long-term prognosis. The impact appears gradually. Older adults who face repeated difficulty may seek care only when symptoms intensify. Preventive visits decline. Acute episodes increase. The healthcare system responds at later stages rather than earlier points of risk.

Institutionalization occurs when these processes become normalized. The digital appointment system ceases to be viewed as a transitional reform. It becomes routine practice. Hospitals organize staffing and workflow around digital booking. Offline channels remain limited. New patients enter an already stabilized structure. Digital competence is treated as an expected attribute rather than a variable condition. The initial mismatch between institutional assumptions and population capacity receives less attention.

At this stage, the digital divide is no longer framed as a temporary adaptation issue. It becomes embedded in everyday operation. The system continues to function smoothly for those who meet procedural demands. Barriers persist for those who do not. Capability difference transforms into durable stratification.

This process demonstrates how institutional design can stabilize inequality without explicit exclusion. Uniform rules apply to all users. The interaction between those rules and uneven capabilities produces differentiated outcomes. When digital ability determines access to medical resources, it also shapes exposure to medical quality and health protection. The digital divide shifts from a technological gap to a structural component of healthcare governance. Once stabilized, it reproduces itself through routine practice.

7. Rebalancing Efficiency and Equity in Aging Societies

7.1 Limits of Pure Efficiency-Oriented Reform

The digital transformation of outpatient services has achieved visible gains in order and administrative control. Patient flow is easier to manage. Appointment data can be tracked. Congestion in hospital halls has decreased in many urban centers. These outcomes reflect the success of efficiency-oriented reform. The system operates in a more predictable manner. Managers can allocate resources with greater precision.

However, the emphasis on efficiency has shaped the value hierarchy of reform. Time savings, measurable output, and standardized procedures occupy the central position. Accessibility and adaptability receive less attention. When efficiency becomes the dominant reference point, design choices tend to favor users who can comply quickly with procedural requirements. Those who require additional time or assistance are treated as exceptions rather than as a core part of the service population.

In an aging society, this imbalance carries structural risk. Older adults represent a growing proportion of outpatient users. If the system assumes uniform digital competence, it places increasing pressure on a population segment with uneven capacity. Efficiency gains for the system may correspond to access barriers for some groups. The reform logic does not openly prioritize one group over another. Yet its design reflects a certain image of the "ideal user" as digitally capable and self-directed.

A governance model centered only on efficiency can overlook long-term equity implications. Medical systems are not only service platforms. They are also public institutions responsible for inclusive access. If procedural speed becomes the main standard, fairness may weaken over time. The tension between efficiency and equity does not require abandoning digital reform. It requires re-examining how values are ordered within institutional design.

7.2 Toward Hybrid and Assisted Access Models

Rebalancing efficiency and equity calls for structural adjustment rather than minor technical fixes. Simplifying interfaces or adding tutorial videos may reduce some difficulty. These steps do not address the underlying assumption that digital self-operation is the normal mode of entry. A more durable response involves redesigning access pathways.

A hybrid access model can combine digital efficiency with stable offline support. Digital booking can remain the primary channel for those who prefer it. At the same time, hospitals can maintain sufficient on-site registration

capacity that does not depend on self-service machines alone. Human assistance desks can function as full substitutes rather than partial guidance points. Offline quotas for high-demand departments can be preserved to ensure that physical presence remains a viable path.

Assisted digital pathways provide another direction. Hospitals may establish structured support roles in which trained staff complete booking procedures on behalf of patients without transferring responsibility entirely to family members. Community health centers can act as intermediary access points, helping older residents secure appointments in higher-level facilities. Such arrangements integrate digital systems into broader care networks instead of isolating them at the hospital gate.

These adjustments do not reverse digital reform. They recalibrate it. The goal is not to remove technological tools but to align institutional design with demographic reality. An aging population requires flexible entry mechanisms. When multiple access routes coexist, digital competence no longer functions as a strict filter. Efficiency remains achievable. Equity becomes structurally protected.

Rebalancing reform in this manner recognizes that digital governance is not neutral. It shapes participation conditions. By adjusting organizational structure rather than focusing only on user adaptation, healthcare systems can reduce the risk that technological change hardens into institutional exclusion.

8. Conclusion

This study has examined how the digital divide among older patients in China's appointment-based outpatient system is produced and stabilized through institutional design. The analysis began by questioning the common explanation that attributes access problems mainly to individual lack of digital skill. It then showed that digital medical reform operates as a restructuring of entry conditions rather than as a simple technological upgrade.

The appointment system is built upon a governance logic that values efficiency, standardization, and data control. Within this logic, digital self-operation becomes an assumed norm. Organizational restructuring relocates the entry point from physical space to digital platforms. Offline alternatives shrink. Procedural completion becomes the prerequisite for medical access. At the micro level, interface complexity, verification demands, and time-sensitive booking mechanisms function as filters. Capability differences are translated into differences in resource acquisition.

Over time, these differences accumulate. Digital competence becomes linked to access to specialist care. Access patterns influence treatment continuity and medical quality. Medical quality differences may shape health outcomes. When these processes become routine, the digital divide is no longer temporary. It becomes embedded in everyday operation. The system appears neutral. Its effects are uneven.

The findings suggest that digital transformation in healthcare cannot be evaluated only by administrative efficiency. In an aging society, institutional assumptions must be examined in relation to population structure. When digital competence functions as a hidden entry condition, exclusion may arise without explicit discrimination. Addressing this issue requires structural recalibration of access pathways rather than simple technical training for older users.

Understanding the digital divide as an institutional outcome shifts the focus from individual adaptation to governance design. It highlights the need to consider how rules, procedures, and organizational arrangements shape participation. Digital systems can improve order and coordination. They also define who can enter smoothly and who faces barriers. The balance between efficiency and equity will determine whether digital reform enhances healthcare access for all groups or consolidates new forms of inequality.

References

Berkman, L. F., Kawachi, I., & Glymour, M. M. (Eds.). (2014). *Social epidemiology* (2nd ed.). Oxford University Press.

Buntin, M. B., Burke, M. F., Hoaglin, M. C., & Blumenthal, D. (2011). The benefits of health information technology: A review of the recent literature. *Health Affairs, 30*(3), 464–471.

Campos-Castillo, C., & Anthony, D. L. (2021). The double-edged sword of electronic health records: Implications for patient trust and healthcare disparities. *Social Science & Medicine, 284*, 114242.

Friemel, T. N. (2016). The digital divide has grown old: Determinants of a digital divide among seniors. *New Media & Society, 18*(2), 313–331.

Gallistl, V., Rohner, R., Seifert, A., & Wanka, A. (2020). Configuring the older non-user: Between research, policy and practice of digital exclusion. *Social Inclusion, 8*(2), 233–243.

Greenhalgh, T., Wherton, J., Shaw, S., & Morrison, C. (2020). Video consultations for COVID-19. *BMJ*, *368*, m998.

Hargittai, E. (2002). Second-level digital divide: Differences in people's online skills. *First Monday, 7*(4).

Helsper, E. J. (2012). A corresponding fields model for the links between social and digital exclusion. *Communication Theory, 22*(4), 403–426.

Kontos, E., Blake, K. D., Chou, W. Y. S., & Prestin, A. (2014). Predictors of eHealth usage: Insights on the digital divide from the Health Information National Trends Survey. *Journal of Medical Internet Research, 16*(7), e172.

Lehoux, P., Miller, F. A., Daudelin, G., & Denis, J. L. (2020). Why health innovation needs equity: A digital health case study. *Globalization and Health, 16*(1), 1–10.

Lupton, D. (2014). Health promotion in the digital era: A critical commentary. *Health Promotion International, 30*(1), 174–183.

Lyles, C. R., Sarkar, U., & Schillinger, D. (2015). Health literacy, vulnerable patients, and health information technology use. *Journal of Health Communication, 20*(Suppl 2), 37–43.

Norris, P. (2001). *Digital divide: Civic engagement, information poverty, and the Internet worldwide*. Cambridge University Press.

Nouri, S., Khoong, E. C., Lyles, C. R., & Karliner, L. (2020). Addressing equity in telemedicine for chronic disease management during the COVID-19 pandemic. *NEJM Catalyst Innovations in Care Delivery, 1*(3).

Oudshoorn, N. (2008). Diagnosis at a distance: The invisible work of patients and healthcare professionals in cardiac telemonitoring technology. *Sociology of Health & Illness, 30*(2), 272–288.

Robinson, L., Cotten, S. R., Ono, H., Quan-Haase, A., Mesch, G., Chen, W., Schulz, J., Hale, T. M., & Stern, M. J. (2015). Digital inequalities and why they matter. *Information, Communication & Society, 18*(5), 569–582.

Seifert, A., Cotton, S. R., & Xie, B. (2020). A double burden of exclusion? Digital and social exclusion of older adults in times of COVID-19. *The Journals of Gerontology: Series B, 76*(3), e99–e103.

Star, S. L., & Ruhleder, K. (1996). Steps toward an ecology of infrastructure: Design and access for large information spaces. *Information Systems Research, 7*(1), 111–134.

van Dijk, J. A. G. M. (2006). Digital divide research, achievements and shortcomings. *Poetics, 34*(4–5), 221–235.

van Dijk, J. A. G. M. (2020). *The digital divide*. Polity Press.