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Design an outline for the review of the neuroactive transdermal drug delivery systems

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ABSTRACT

Background: Transdermal drug delivery began in the 1960s with skin absorption studies, leading to the commercialisation of scopolamine and nitroglycerin patches in the 1970s to maintain steady drug levels. Oral MAOIs carry severe risks, such as tyramine-induced hypertensive crises, prompting alternative approaches. Selegiline, a selective MAO-B inhibitor, was reformulated as a transdermal patch to bypass first-pass metabolism, achieving brain therapeutic levels with reduced peripheral exposure.

Methods: A comprehensive systematic literature search identified 21 potential drug candidates suitable for transdermal delivery. Among these, several agents emerged as particularly promising due to their pharmacokinetic properties and therapeutic relevance. Notable examples in the clinical trial stage includes citalopram, the combination of bupropion with nortriptyline, nicotine, selegiline, ketamine, sertraline, rivastigmine, raloxifene, buprenorphine, fluoxetine, and rotigotine. These drugs are considered ideal candidates for transdermal drug delivery systems because they can benefit from bypassing gastrointestinal metabolism, reducing systemic side effects, and maintaining steady plasma concentrations. Collectively, the findings highlight a diverse range of psychotropic, neuroactive, and analgesic compounds that may be optimised through patch-based or assisted transdermal technologies, underscoring the growing interest in expanding beyond traditional oral and injectable routes.

Result and Conclusion: A systematic review found that selegiline, Rivastigmine, and rotigotine have received US FDA/EU approval in transdermal patch form.

Keywords: *Anti-depressant, Anti-pychotic, Parkinson's disease, transdermal drug delivery system, Clinical trial, First-pass metabolism and Neuroactive.*

1. INTRODUCTION

Neuroactive therapeutics—including analgesics, antidepressants, antiepileptics, antiparkinsonian agents, and drugs designed to address neurodegenerative pathways—represent a fundamental pillar of contemporary neurological and psychiatric treatment. [1] Yet, their clinical effectiveness is often constrained by the limitations of conventional oral and parenteral delivery methods. Factors such as extensive first-pass metabolism, instability within the gastrointestinal tract, variable plasma concentrations, and the invasiveness of certain dosing routes can undermine both therapeutic outcomes and patient compliance. In addition, the physicochemical characteristics of many neuroactive compounds impede efficient penetration into the central nervous system (CNS). These challenges underscore the urgent need for innovative, patient-friendly delivery strategies that can enhance efficacy and broaden the utility of neuropharmacological interventions. [2]

Transdermal drug delivery systems (TDDS) present an attractive alternative by facilitating the controlled passage of therapeutics through the skin into systemic circulation. Over the last twenty years, these platforms have evolved beyond conventional patch technologies into advanced, bioengineered constructs that integrate chemical penetration enhancers, microneedles, nanocarriers, and stimuli-responsive materials. Such innovations have broadened the spectrum of neuroactive agents amenable to transdermal administration while simultaneously enhancing pharmacokinetic accuracy through sustained and programmable release profiles. [3]

For neuroactive agents, transdermal drug delivery systems (TDDS) offer distinct therapeutic advantages. By stabilising plasma concentrations, they help mitigate systemic side effects, while reduced dosing frequency and the ability to bypass hepatic metabolism contribute to improved patient adherence—particularly in the management of chronic neurological conditions. Furthermore, emerging TDDS technologies are being engineered to enable targeted delivery to the central nervous system (CNS), addressing persistent challenges such as inconsistent blood–brain barrier (BBB) penetration. With

ongoing advances, transdermal platforms are increasingly coupled with wearable sensors and digital health technologies, paving the way for closed-loop, personalised neurotherapeutic solutions. [4]

For neuroactive therapeutics, transdermal delivery provides a means of achieving targeted and sustained release, thereby maintaining stable drug concentrations within the central nervous system. This approach is particularly valuable for the long-term management of neurological disorders such as Alzheimer's disease, Parkinson's disease, depression, and other neuropsychiatric conditions. Recent innovations—including dissolvable microneedle patches and nanocarrier-based systems—have been designed to improve skin penetration of neuroactive agents while reducing the risk of local irritation and allergic responses. [5, 6]

This review offers a comprehensive synthesis of both established and emerging transdermal drug delivery systems (TDDS) for neuroactive agents. It explores pharmacological factors specific to neuroactive compounds, evaluates current and experimental transdermal technologies, and examines strategies designed to enhance skin permeation and central nervous system (CNS) targeting. The article also highlights recent clinical advances in the field. Finally, it addresses existing challenges and outlines future directions necessary to fully harness the potential of TDDS in treating neurological and psychiatric disorders. [7]

2. LITERATURE REVIEW

MARKETED TRANSDERMAL DRUG DELIVERY SYSTEM THAT ACTS ON NEURONS

The rotigotine transdermal patch (Neupro), a non-ergoline dopamine agonist, is approved for the treatment of neurological disorders, including both early and advanced stages of Parkinson's disease as well as Restless Legs Syndrome. By delivering rotigotine continuously over 24 hours, the patch maintains stable plasma—and likely central nervous system—concentrations. [8, 9] The rivastigmine patch (Exelon), a cholinesterase inhibitor, is indicated for dementia associated with Alzheimer's disease and Parkinson's disease. Its transdermal format enhances tolerability by reducing gastrointestinal side effects compared with oral administration. [10, 11, 12] The selegiline transdermal system (Emsam), a monoamine oxidase inhibitor (MAOI), is approved for Major Depressive Disorder and exemplifies how bypassing first-pass metabolism through transdermal delivery markedly improves bioavailability relative to oral dosing. [13, 14] In addition, partially CNS-acting systems such as clonidine, fentanyl, and buprenorphine patches illustrate the broader therapeutic utility of transdermal delivery for agents that modulate neuronal activity via peripheral or central pathways, particularly in pain management and autonomic regulation. [15, 16, 17] Collectively, these examples highlight the versatility of transdermal drug delivery systems (TDDS) in meeting unmet needs across neurological, psychiatric, and neurophysiological conditions. [18]

In recent years, the global transdermal patch market has generated approximately USD 6–7 billion annually. If one assumes—optimistically—that 10–20% of this market is attributable to patches with neuroactive or CNS-acting properties, the estimated revenue for such products would fall in the range of USD 600–1,400 million per year. [19, 20, 21, 22, 23, 24] Extrapolated over five years, this corresponds to a cumulative market value of roughly USD 3–7 billion.

Table 1 Sales Data for branded transdermal products

Name of Product	Yearly Sales in USD	Compound annual growth rate (CAGR) (%)
Neupro	649.4 million	5.5
Exelon	129 million	7.1
Emsam	141.6 million	4.9
Catapres	1.5 billion	5-6
Duragesic	1.5 billion	5.4
Burtrans	800 million	5.9

DRUGS IN ADVANCE CLINICAL STAGE

Major depressive disorder (MDD) affects more than 280 million individuals globally [25], representing a profound public health challenge that necessitates treatment strategies extending beyond traditional oral antidepressants. Although oral agents remain the most common therapeutic option, they are frequently associated with significant drawbacks, including poor adherence rates approaching 50%, gastrointestinal adverse effects, inconsistent bioavailability due to first-pass hepatic metabolism, and plasma level fluctuations that can compromise efficacy or increase toxicity. Transdermal drug delivery systems (TDDS) offer a promising alternative by enabling controlled, sustained release of medication through the skin,

thereby maintaining stable plasma concentrations, improving compliance with once-daily or weekly dosing, and avoiding gastrointestinal degradation. Effective transdermal absorption requires overcoming the barrier function of the stratum corneum, often achieved through specialised matrix or reservoir patch designs incorporating permeation enhancers, particularly for lipophilic compounds such as selegiline.

The selegiline transdermal system (EMSAM or STS), approved by the FDA in 2006, remains the only antidepressant patch currently available. As a monoamine oxidase inhibitor (MAOI), it selectively inhibits MAO-B at lower doses (6 mg/24h) and provides dual MAO-A/B inhibition at higher therapeutic doses (9–12 mg/24h), reducing peripheral risks such as the tyramine-induced "cheese reaction." This innovation revitalises the clinical utility of MAOIs, which were historically constrained by dietary restrictions and adverse events, and demonstrates efficacy in treatment-resistant, atypical, and anxious depression subtypes. [26, 27]

Despite its advantages, EMSAM has seen limited adoption, accounting for less than 0.1% of antidepressant prescriptions, largely due to factors such as patch-related skin irritation and the absence of additional approved options. Current research is investigating new transdermal formulations for agents like citalopram, employing advanced technologies including microneedles, iontophoresis, and vesicular carriers to improve permeability for hydrophilic drugs. This review, therefore, explores the pharmacokinetics, clinical evidence, formulation strategies, and future directions of transdermal antidepressant systems, emphasising their potential role in advancing precision psychiatry. [28]

Dissolving microneedle patches for paroxetine HCl underwent in vitro/ex vivo studies and PBPK modelling in 2025, demonstrating enhanced bioavailability over oral forms without clinical efficacy trials yet. [29] Citalopram hydrobromide transdermal systems showed sustained 24-hour release, higher AUC, and no skin irritation in pharmacokinetic validation studies. [30] Transdermal nicotine patches exhibited antidepressant effects in small trials for non-smoking MDD patients, with significant HAM-D improvements after 2-4 days but relapse post-treatment. [31]

Rotigotine transdermal patches for Parkinson's disease (dopamine agonist with neuropsychiatric benefits) succeeded in phase III trials despite higher application-site reactions. Rivastigmine patches for Alzheimer's (cholinesterase inhibitor) completed bioequivalence trials like NCT03573050. [32] Emerging antipsychotics include weekly aripiprazole [33] and daily asenapine patches, with phase I bioavailability studies confirming sustained delivery but no phase III completion for psychiatry indications. No new 2025 approvals noted beyond EMSAM.

Asenapine transdermal patch (Secuado) gained FDA approval in 2021 for schizophrenia based on a 6-week, double-blind, placebo-controlled phase III trial (N=607) showing superior Positive and Negative Syndrome Scale (PANSS) improvements versus placebo, alongside Clinical Global Impressions-Severity (CGI-S) benefits. [34] Blonanserin transdermal patch (Lonasen Tape) received approval in Japan in 2019 for schizophrenia, supported by pharmacokinetic and efficacy data demonstrating tolerability and adherence advantages over oral forms. [35, 36]

A 2025 retrospective cohort study compared blonanserin patch efficacy to oral formulation in schizophrenia patients, finding comparable symptom control with better acceptability in acute settings. Risperidone matrix-type transdermal patches underwent 2025 pilot pharmacokinetic studies in rabbits, confirming sustained release, comparable bioavailability to oral dosing, minimal skin irritation, and stability over three months per ICH guidelines. Earlier acceptability trials (2019-2021) in delirium patients refusing oral meds showed 95% acceptance of blonanserin patches, with lower delirium recurrence (24.5% vs. 100% in refusers) over 2 weeks. A multi-centre, randomised, double-blind, placebo-controlled phase 3 trial (N=580) across Japan and other countries evaluated blonanserin transdermal patch (40 mg/day and 80 mg/day) versus placebo in acute schizophrenia patients, showing significant PANSS total score improvements at week 6 (LS mean difference -5.6 for 40 mg) with good tolerability and mild skin reactions. A Japan-specific phase 3 study included a 6-week double-blind phase followed by open-label extension, confirming early efficacy from week 1 and sustained PANSS reductions. [37]

Formulation studies for second-generation antipsychotics like risperidone emphasise controlled delivery to enhance adherence, with in vitro/ex vivo permeation tests and animal models indicating prolonged mean residence time and reduced dosing frequency. [38] No additional phase III trials or 2025 approvals beyond asenapine and blonanserin were reported, though transdermal systems show promise for non-compliant psychiatric populations.

Table 2 Completed clinical studies related to transdermal systems [39]

Sr. No.	NCT Number	Study Title	Conditions	Interventions
1	NCT00271453	A Study to Assess the Safety and Effectiveness of Durogesic (Fentanyl Transdermal Patch) in the Treatment of Children With Chronic Pain Requiring Long-term Narcotic Pain Relief Therapy	Chronic Pain	Durogesic® (fentanyl transdermal drug delivery system)
2	NCT01476774	NORSPAN Transdermal Patches Phase III Study In	Intervertebral Disc, With	Buprenorphine Transdermal

Sr. No.	NCT Number	Study Title	Conditions	Interventions
		Non-Cancer Pain	Myelopathy (Manifestation)	System Buprenorphine Transdermal System
3	NCT00586157	Study of Medication Patch to Treat Children Ages 6-12 With ADHD	Attention Deficit Hyperactivity Disorder	Methylphenidate Transdermal System Placebo
4	NCT00549601	Convenience, Tolerability, and Safety of Change in the Administration of Rivastigmine From Capsules to a Transdermal Patch in Patients With Mild to Moderate Alzheimer's Disease	Alzheimer's Disease	Rivastigmine patch (4.6 mg/day switch to 9.5 mg/day) Rivastigmine patch (9.5 mg/day) Rivastigmine capsules (6 mg to 12 mg/day)
5	NCT00099242	Efficacy and Safety of the Rivastigmine Transdermal Patch in Patients With Probable Alzheimer's Disease	Alzheimer's Disease Dementia	Rivastigmine transdermal patch
6	NCT00423085	Efficacy and Safety of Rivastigmine Transdermal Patch in Patients With Mild to Moderate Alzheimer's Disease	Alzheimer's Disease	Rivastigmine transdermal patch Placebo
7	NCT00219232	An Open-label Extension to Evaluate the Efficacy and Safety of the Rivastigmine Transdermal Patch in Patients With Probable Alzheimer's Disease	Alzheimer's Disease	Rivastigmine Transdermal Patch
8	NCT00724815	The Efficacy and Tolerability of NP101 Patch in the Treatment of Acute Migraine	Migraine Disorders	NP101 – S Sumatriptan iontophoretic transdermal patch Placebo
9	NCT01252160	Safety and Effectiveness of Repeated Administration of QUTENZA Patches for Treatment of Pain Caused by Nerve Damage	Neuralgia, Post herpetic	QUTENZA
10	NCT01292642	Cognitive Behavioural Therapy and the Nicotine Transdermal Patch for Cannabis Dependence and Nicotine Dependence	Cannabis Dependence Nicotine Dependence	BEHAVIORAL: Cognitive Behavioral Therapy Nicotine Replacement Therapy
11	NCT01585272	Tolerability of Rivastigmine Before and After Switching From Oral Formulation to Transdermal Patch in Alzheimer's Dementia	Alzheimer's Dementia	ENA713

Sr. No.	NCT Number	Study Title	Conditions	Interventions
12	NCT01670526	Rivastigmine Patch in Veterans With Cognitive Impairment Following TBI	Traumatic Brain Injury Cognitive Impairment	Rivastigmine Transdermal Patch
13	NCT00428389	Safety of Switching From Donepezil to Rivastigmine Patch in Patients With Probable Alzheimer's Disease	Alzheimer's Disease	Rivastigmine 5 cm^2 transdermal patch 10 cm^2 transdermal patch
14	NCT00731224	Compliance and Tolerability of Rivastigmine Transdermal Patch 10 cm^2 in Patients With Probable Alzheimer's Disease.	Alzheimer's Disease	Rivastigmine transdermal patch
15	NCT01529619	Efficacy, Safety and Tolerability of Rivastigmine Patch in Patients With Mild to Moderate Alzheimer's Disease Switched From Cholinesterase Inhibitors	Alzheimer's Disease	Rivastigmine transdermal patch
16	NCT00594464	A Trial of Neupro® (Rotigotine Transdermal Patch) in Patients With Parkinson's Disease Undergoing Surgery	Parkinson's Disease	Rotigotine
17	NCT00271466	A Study to Assess the Safety, Dose Conversion, and Dose Individualization of Duragesic® (Fentanyl Transdermal Patch) in the Treatment of Children With Chronic Pain Requiring Narcotic Pain Relief Therapy	Chronic Pain	Duragesic® (fentanyl) Therapeutic Transdermal System (TTS)
18	NCT00478179	Study of a Bupivacaine Patch to Treat Post- Herpetic Neuralgia	Post herpetic Neuralgia Pain	Transdermal/Patch (Bupivacaine TTS)
19	NCT03197740	A Multinational, Multi-center, Randomized, Double-blind, Active Comparator, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Donepezil Transdermal Patch in Patients With Alzheimer's Disease	Alzheimer Disease	Donepezil patch DRUG: aricept Tab
20	NCT04189666	Rivastigmine Patch Compared to Melatonin Patch in Prevention of Postoperative Delirium	Delirium	Rivastigmine Transdermal System Exelon DRUG: Melatonin
21	NCT00522379	Trial to Assess Parkinson's Disease (PD) Symptom Control to Four Doses of Rotigotine in a Transdermal Patch	Parkinson's Disease	Rotigotine Placebo
22	NCT06247410	Clinical Trial to Investigate Patch Adhesion of Rotigotine Containing Patches in Patients With Parkinson's Disease	Parkinson Disease	Rotigotine 8Mg/24Hrs Patch
23	NCT00622713	A 24 Week, Multicenter, Open, Evaluation of the Clinical Effectiveness of the Once-daily 10 cm^2 Rivastigmine Patch Formulation in Patients With Probable Alzheimer's Disease (EXTRA)	Alzheimer's Disease	Rivastigmine transdermal patch
24	NCT00089622	Lisuride Patch to Treat Parkinson's Disease	Parkinson Disease	Intravenous Levodopa

Sr. No.	NCT Number	Study Title	Conditions	Interventions
				Lisuride Transdermal System
25	NCT01902524	Efficacy and Safety Study of Fentanyl Transdermal Patch for Treatment of Chronic Pain	Chronic Pain	Fentanyl-TTS
26	NCT00013585	Safety and Effectiveness of the Selegiline "Patch" for Decreased Mental Function in HIV Patients	Cognition Disorders HIV Infections	Selegiline hydrochloride
27	NCT00271414	A 15-day Study to Assess the Safety and Clinical Utility of Duragesic (Fentanyl Transdermal Patch) in the Treatment of Children With Continuous Pain Requiring Narcotic Pain Relief Therapy	Chronic Pain	Duragesic® (fentanyl) Transdermal Therapeutic System (TTS)
28	NCT02989402	A Phase IV Study to Evaluate Safety, Tolerability and Effectiveness of Rivastigmine Patch 15 cm^2 in Patients With Severe Dementia of the Alzheimer's Type.	Alzheimer's Disease	Rivastigmine
29	NCT01047579	A 12 Week, Multicenter, Open Label Evaluation of Caregiver Preference, Safety and Tolerability of Exelon® Patch (Rivastigmine Transdermal) in Patients With Alzheimer's Disease	Alzheimer's Disease	Rivastigmine transdermal
30	NCT01025466	Exelon Patch and Combination With Memantine Comparative Trial	Alzheimer's Disease	Rivastigmine transdermal patch (Exelon patch), memantine Rivastigmine transdermal patch
31	NCT00623103	Long-term Safety of Rivastigmine Capsule and Patch in Patients With Mild to Moderately-severe Dementia Associated With Parkinson's Disease (PDD)	Parkinson's Disease Dementia	Rivastigmine capsule Rivastigmine transdermal patch
32	NCT01537042	A Sleep Laboratory Study to Investigate the Safety and Efficacy of the Rotigotine Skin Patch in Subjects With Restless Legs Syndrome and End-Stage Renal Disease Requiring Hemodialysis	Restless Legs Syndrome End-Stage Renal Disease	Rotigotine Placebo
33	NCT00243945	A Trial to Evaluate the Effects of Rotigotine Transdermal Patch on Early Morning Motor Impairment and Sleep Disorders Idiopathic Parkinson's Disease	Idiopathic Parkinson's disease	Rotigotine
34	NCT00506415	Comparative Efficacy, Safety, and Tolerability of Rivastigmine 10 and 15 cm^2 Patch in Patients With Alzheimer's Disease (AD) Showing Cognitive Decline	Alzheimer Disease	Rivastigmine 5 cm^2 Rivastigmine 10 cm^2 Rivastigmine 15 cm^2 Placebo to 15 cm^2 patch

Sr. No.	NCT Number	Study Title	Conditions	Interventions
				Placebo to 10 cm^2 patch
35	NCT01614886	Randomized, Double-blind Study to Evaluate the Tolerability of 2 Different Titration Methods of Rivastigmine Patch in AD Patients (MMSE 10-20)	Alzheimer's Disease	Active Comparator: ENA713
36	NCT00243971	A Trial to Compare the Efficacy of Rotigotine Transdermal Patch to That of Ropinirole on Early Morning Motor Impairment and Sleep Disorders in Subjects With Early-Stage, Idiopathic Parkinson's Disease	Parkinson's Disease	SPM 962
37	NCT01399125	A 24-Week Efficacy, Safety and Tolerability of Rivastigmine Patch Study in Patients With Probable Alzheimer's Disease	Alzheimer's Disease	Rivastigmine Patch Placebo to Rivastigmine capsules
38	NCT01711866	A Phase 4, Open-label Study to Assess the Feasibility and Efficacy on Motor and Non-motor Symptoms of Switching From Pramipexole or Ropinirole to Rotigotine Transdermal Patch in Subjects With Advanced Idiopathic Parkinson's Disease	Advanced Idiopathic Parkinson's Disease	Rotigotine
39	NCT00948766	Effects of Rivastigmine Patch on Activities of Daily Living and Cognition in Patients With Severe Dementia of the Alzheimer's Type (ACTION) (Study Protocol CENA713DUS44, NCT00948766) and a 24 Week Open-label Extension to Study CENA713DUS44	Alzheimer's Disease	Rivastigmine 4.6 mg/24 h (5 cm^2) Rivastigmine 9.5 mg/24 h (10 cm^2) Rivastigmine 13.3 mg/24 h (15 cm^2) Placebo
40	NCT03380533	Buprenorphine Transdermal Patches in Arthroscopic Rotator Cuff Repair	Rotator Cuff Tear Rotator Cuff Injury Analgesics, Opioid Buprenorphine	Buprenorphine Placebo Patch Multimodal Oral Scheme Tramadol, Placebo Tablet
41	NCT01416116	Method of Pre-treatment for Application of QUTENZA Capsaicin 8% Patch	Peripheral Nerve Injury (PNI) Peripheral Neuropathic Pain (PNP) Due to Post herpetic Neuralgia (PHN)	QUTENZA Lidocaine Tramadol

POTENTIAL NEUROACTIVE CLASS OF DRUGS FOR TRANSDERMAL DRUG DELIVERY SYSTEM

Atypical Antipsychotics

Trazodone, a moderately lipophilic antipsychotic (log P ~2.7–2.9), demonstrates favourable aqueous solubility (~290 mg/L) and moderate oral bioavailability of 65–80%. It exhibits extensive plasma protein binding (~90%) and undergoes substantial metabolism via the cytochrome P450 (CYP) enzyme system. [40] In contrast, nefazodone is characterised by poor aqueous

solubility and low lipophilicity (log P 0.2–0.9), coupled with very high plasma protein binding (~99%). Its oral bioavailability is markedly reduced (~20%) due to extensive first-pass metabolism, primarily mediated by CYP_3A_4 and CYP_2D_6. [41] Mirtazapine distinguishes itself with high solubility (~1.1 g/L) and moderate lipophilicity (log P ~3.0), alongside 85% plasma protein binding and approximately 50% bioavailability. It is extensively metabolised by CYP_1A_2, CYP_2D_6, and CYP_3A_4 and possesses a prolonged half-life of 20–40 hours. [42] Collectively, these pharmacokinetic and physicochemical attributes are pivotal in the rational design of transdermal delivery systems, as parameters such as lipophilicity, solubility, protein binding, metabolic pathways, and bioavailability critically determine skin permeation and systemic exposure of antipsychotic agents administered via the transdermal route.

Monoamine oxidase inhibitors (MAO)

The physicochemical and pharmacokinetic properties of monoamine oxidase inhibitors (MAOIs) play a decisive role in determining their suitability for transdermal delivery. Selegiline, characterised by high lipophilicity (log P ~2.7–3.1), strong plasma protein binding (85–90%), and appreciable water solubility, is particularly amenable to passive diffusion across the stratum corneum. Its low oral bioavailability (4–10%) resulting from extensive CYP-mediated first-pass metabolism, combined with a steady-state half-life of ~10 hours, further highlights the advantages of circumventing gastrointestinal and hepatic metabolism via the transdermal route. [43] By contrast, isocarboxazid demonstrates moderate lipophilicity (log P ~1.2–1.5) and relatively high aqueous solubility (~800 mg/L), yet its short elimination half-life (~1.5–4 hours) and rapid hepatic conversion to hippuric acid yield poor oral bioavailability and limit its ability to sustain stable plasma concentrations through transdermal transport without enhancement strategies. [44] Phenelzine, although highly water-soluble (~29 g/L) and only modestly lipophilic (log P ~1.1), exhibits a longer half-life (~11.6 hours) and undergoes extensive hepatic oxidative metabolism, with metabolites largely excreted in urine. [44, 45] While its hydrophilicity poses challenges for passive transdermal flux, its pharmacokinetic stability suggests that engineered approaches—such as microneedle arrays or chemical enhancer–based patches—may help overcome these barriers. Taken together, these profiles explain why selegiline has become the prototype MAOI for transdermal delivery, whereas isocarboxazid and phenelzine are more likely to require advanced penetration-enhancing technologies to achieve therapeutic efficacy

Serotonin-norepinephrine reuptake inhibitor (SNRI)

Duloxetine, a lipophilic serotonin–norepinephrine reuptake inhibitor (SNRI) with moderate aqueous solubility (~2.96 mg/L), exhibits extensive plasma protein binding and undergoes significant hepatic metabolism, primarily mediated by CYP_2D_6 and CYP_1A_2. [46] Venlafaxine, by contrast, is more hydrophilic (<100 mg/L solubility) with low lipophilicity (log P ~0.4), moderate protein binding, and a relatively short half-life of about 5 hours in its immediate-release form. It is extensively metabolised to its active metabolite, chiefly via CYP_2D_6. [47] Levomilnacipran differs markedly, displaying high aqueous solubility (~1.23 g/L), low lipophilicity (log P ~1.4–1.7), minimal protein binding, a prolonged half-life (~12 hours), and excellent oral bioavailability (~92%), with metabolism primarily through CYP_3A_4. [48] Collectively, these physicochemical and pharmacokinetic attributes are critical in guiding the design of transdermal formulations, as factors such as solubility, lipophilicity, protein binding, metabolic pathways, and bioavailability directly influence skin permeation, systemic stability, and the potential to bypass first-pass metabolism in SNRI-based neurotherapeutic delivery systems.

Selective serotonin reuptake inhibitor (SSRI)

Selective serotonin reuptake inhibitors (SSRIs) display diverse physicochemical and pharmacokinetic properties that shape their potential for transdermal delivery. Their molecular weights fall within the range generally considered favourable for skin permeation—Fluoxetine (309 Da), Paroxetine (329 Da), Citalopram and its S-enantiomer Escitalopram (~324 Da), and Sertraline (~306 Da). Solubility and lipophilicity, however, vary widely. Fluoxetine exhibits relatively low aqueous solubility (~14 mg/L), [49] whereas Paroxetine is markedly more soluble (~5400 mg/L at 25 °C) and demonstrates log P values of ~2.5–3.9, supporting efficient skin partitioning. [50] Sertraline, with a basic pKa of ~9.16 and high lipophilicity, may encounter ionisation-dependent permeability challenges in the mildly acidic stratum corneum. [51] Despite these differences, SSRIs consistently show high plasma protein binding—Fluoxetine ~95%, Paroxetine ~93–95%, Sertraline ~98.5%, with Escitalopram as a notable exception at ~56%—a feature that often facilitates depot-like, sustained release following transdermal absorption. [52] Their extended half-lives (Fluoxetine 4–6 days; norfluoxetine up to 16 days; Citalopram ~35 h; Escitalopram ~27–33 h; Paroxetine ~21 h; Sertraline ~26 h) and moderate-to-high oral bioavailability (Fluoxetine 70–90%, Paroxetine ~50%, Citalopram ~80%) lessen the immediate need for alternative routes, yet also suggest that transdermal systems could maintain stable plasma concentrations at relatively low delivery rates. All SSRIs undergo extensive hepatic metabolism—primarily via CYP_2D_6, CYP_2C_{19}, and CYP_3A_4—making transdermal administration particularly advantageous for bypassing first-pass metabolism, reducing inter individual variability, and potentially minimising drug–drug interactions. Overall, while physicochemical challenges such as low solubility or ionisation behaviour may necessitate formulation enhancements, the pharmacokinetic features of SSRIs strongly support the exploration of transdermal platforms to improve tolerability, adherence, and long-term therapeutic consistency.

Tricyclic antidepressant (TCA)

Tricyclic antidepressants (TCAs) possess physicochemical and pharmacokinetic properties that present both opportunities and challenges for transdermal drug delivery. Their solubility profiles vary widely: amitriptyline's free base is only sparingly soluble in water (~2 mg/L), while its hydrochloride salt displays markedly enhanced solubility (>1000 mg/L under acidic conditions), and desipramine exhibits moderate solubility (~40 mg/L. [53, 54] Quantitative solubility data for other TCAs are limited, but the class is generally characterised by high lipophilicity, with desipramine showing a representative log P of ~4. The basic nature of TCAs—exemplified by amitriptyline's pKa of ~9.45—suggests that ionisation in the mildly acidic stratum corneum may restrict passive diffusion, making formulation strategies that enhance membrane partitioning particularly relevant. [55] Pharmacokinetically, most TCAs have elimination half-lives in the 12–30 hour range, with certain active metabolites persisting even longer, contributing to their prolonged therapeutic effects. All members of the class are extensively protein-bound (>80%, and often >90%), a feature that supports sustained systemic exposure once transdermal absorption is achieved. Oral bioavailability is moderate to high—approximately 45–53% for amitriptyline and 60–70% for desipramine—yet highly variable due to pronounced hepatic first-pass metabolism. Like many centrally acting lipophilic agents, TCAs undergo extensive biotransformation by multiple CYP isoforms, most commonly CYP_2D_6, CYP_1A_2, CYP_3A_4, and CYP_2C_{19}, contributing to significant interindividual variability and drug–drug interaction potential. Taken together, the lipophilicity, long half-lives, and high protein binding of TCAs are favourable for transdermal delivery, whereas their ionisation behaviour and metabolic complexity indicate that advanced formulation approaches—such as chemical enhancers, ion-pair strategies, or microneedle-assisted systems—may be necessary to optimise their transdermal performance.

Table 3 Neuroactive drug properties suitable for a transdermal drug delivery system

Sr. No.	Drug	MW (g/mol)	Solubility (mg/L)	log P	pKa	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Oral Bioavailability (%)	Hepatic Metabolism & Extent
1	Trazodone	371.9	~290 mg/L (0.29 mg/mL)	2.68–2.9	~6.74–7.09	4–15 h for parent; metabolites 9–16 h	89–95 %	65–80 %	Extensive: primarily CYP3A4; also CYP2D6, CYP1A2
2	Nefazodone	444.0	"Sparingly soluble" (poor solubility)	0.22–0.87	≈6.4	2–4 h (parent); metabolites up to 18 h	~99 % (loose binding)	~15–23 % (20 % average)	Extensive: CYP3A4 predominant; also CYP2D6; extensive first-pass (74–87 %)
3	Mirtazapine	265.35	~1,100 mg/L	~2.9–3.2	~6.67	20–40 h (occasionally up to 65 h)	~85 %	~50 %	Extensive: CYP1A2, CYP2D6, CYP3A4 metabolism (~100% metabolized)
4	Isocarboxazid	231.25	~800 mg/L in water at 25 °C	~1.2–1.5	~10.4	1.5–4 h	—	Low (peak at 1–2 h; likely <10 %)	Extensive hepatic via carboxylesterase and oxidation; rapid 1st-pass; excreted primarily as hippuric acid (~42% in urine)
5	Phenelzine	~136 ($C_{11}H_{12}N_2O$)?	~29,100 mg/L (29.1 g/L)	~1.1–1.2	~5.55	~11.6 h	—	Rapid absorption; bioavailability not specified but typical for MAOIs	Extensively metabolized in liver; oxidation is primary route; metabolites excreted in urine (~73% over 96 h)

Sr. No.	Drug	MW (g/mol)	Solubility (mg/L)	log P	pKa	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Oral Bioavailability (%)	Hepatic Metabolism & Extent
6	Duloxetine	333.9 (HCl, API)	~2.96 mg/L	~4.0	≈ 9.7 (basic)	~12 h (range 10–12 h)	> 90 %	~50 % (range 30–80 %)	Extensive; CYP2D6 & CYP1A2 (> 90 % metabolism) (pmc.ncbi.nlm.nih.gov, formulationdiary.com, invivochem.com)
7	Venlafaxine	277.4	< 0.1 g/L (i.e., < 100 mg/L)	~0.4	≈ 9.4–9.5	5 ± 2 h (IR); 15 ± 6 h (ER); active metabolite ~11 h	27 ± 2 %	~42 ± 15 %	Extensive; primarily CYP2D6 → O-desmethylvenlafaxine
8	Levomilnacipran	255.3 (free base; formula C15H22N2O)	~1.23 mg/mL (1,230 mg/L)	~1.4–1.7	≈ 9.83	~12 h	22 %	92 %	Metabolism mainly by CYP3A4; moderate other CYPs
9	Citalopram	~324	—	—	—	~35 h	—	~80 % (pmc.ncbi.nlm.nih.gov)	~80 %
10	Escitalopram	~324	—	—	—	27–33 h	56 %	—	Extensive via CYP2C19/2D6/3A4
11	Fluoxetine	309.3	14 mg/L	—	—	96–144 h (4–6 days); norfluoxeti	~95 %	70–90 %	Extensive CYP2D6 → norfluoxetine

Sr. No.	Drug	MW (g/mol)	Solubility (mg/L)	log P	pKa	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Oral Bioavailability (%)	Hepatic Metabolism & Extent
						ne 168–384 h			
12	Paroxetine	329.4 (free base)	5.4 mg/mL (5400 mg/L)	~2.5–3.9 range	~9.9	~21 h (range 7–65)	93–95 %	~50 % (30–60 %)	Extensive CYP2D6 first-pass
13	Sertraline	~306	—	—	~9.16	~26 h (13–45)	98.5 %	—	Extensive first-pass (multiple CYPs)
14	Amoxapine	~401 (HCl salt)	—	—	—	~8 h	~90 % (en.wikipedia.org, en.wikipedia.org)	—	Extensive hepatic (~60% excreted urine; likely CYP2D6)
15	Amitriptyline	313.9 (HCl)	Free base ~2 mg/L; HCl salt "freely soluble" – ~1000 mg/L at pH 1.2	High (lipophilic)	9.45	21 h (10–28 range)	96 %	45–53 %	Extensive via CYP2C19, CYP2D6, CYP3A4 (>90 %)
16	Maprotiline	~278	—	—	—	~32 h	~90 %	—	Hepatic (likely CYP pathways)
17	Desipramine	302.8	~40 mg/L (~0.04 g/L)	~4.0–4.9	~10.0	12–30 h	91 %	60–70 %	Extensive via CYP2D6 & CYP1A2
18	Nortriptyline	279.4	—	—	—	~30–90 h*	>90 %	—	Extensive hepatic (likely CYP2D6)

Sr. No.	Drug	MW (g/mol)	Solubility (mg/L)	log P	pKa	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Oral Bioavailability (%)	Hepatic Metabolism & Extent
19	Doxepin	279.4	—	—	—	~18 h (30 h metabolite)	~80 %	—	CYP2D6, CYP2C19, CYP3A4 metabolism
20	Trimipramine	299.4	—	—	—	~32 h	~>90 %	—	Hepatic (CYP-mediated)
21	Imipramine	280	—	—	—	~12 h (30 h metabolite)	~90 %	High	CYP1A2, CYP2C19, CYP2D6 metabolism

WHY TRANSDERMAL PATCHES STRUGGLE WITH NEUROACTIVE DRUGS

Transdermal drug delivery for neuroactive compounds faces numerous challenges, as consistent therapeutic plasma levels are critical due to narrow therapeutic windows, yet variability in skin permeability across patients leads to inconsistent pharmacokinetics. Inter-patient differences in age, hydration, skin thickness, disease states, and application site further contribute to systemic exposure variability, while long-term patch use often results in dermatitis, erythema, sensitisation, or adhesive intolerance, particularly when enhancers are required. Many CNS drugs demand relatively high doses that exceed the limited daily delivery capacity of patches, and even when systemic levels are achieved, poor blood–brain barrier penetration frequently undermines clinical efficacy. Real-world conditions such as sweating, showering, and physical activity can cause patch detachment, leading to dose dumping or sub-therapeutic exposure, complicating trial outcomes. Safety concerns, including risks of misuse, tampering, accidental pediatric exposure, and overdose, attract regulatory scrutiny and necessitate additional studies. Moreover, the slow onset of action inherent to transdermal systems is unsuitable for acute conditions requiring rapid symptom control, while patient compliance issues—such as incorrect placement, replacement timing, or impaired adherence in psychiatric populations—further hinder success. Demonstrating superiority over established, inexpensive oral therapies is difficult, as trials must show clear advantages in side effects, pharmacokinetics, or adherence, and large-scale manufacturing introduces variability in drug release that can affect both safety and efficacy data. Transdermal delivery systems for neuroactive drugs encounter significant sustainability challenges, primarily driven by high development and manufacturing costs, intense competition from well-established oral formulations, and substantial variability in patient response. To achieve long-term market viability, these products must not only overcome technical and regulatory hurdles but also demonstrate clear and measurable advantages over conventional CNS delivery routes. Such advantages should encompass superior therapeutic outcomes, improved tolerability, enhanced patient convenience, and compelling economic value, thereby justifying their use in a landscape dominated by inexpensive and widely accepted oral therapies.

Table 4 Most impacting factors for Transdermal Drug Delivery System

Sr. No.	Impacting Factor	Insight
1	Skin Barrier Limitations	The stratum corneum presents a formidable barrier; many neuroactive drugs are large, hydrophilic, or ionized, thereby limiting passive diffusion
2	Dose Constraints	CNS therapeutics often require high plasma concentrations, yet transdermal systems deliver only small daily doses, restricting applicability to drugs with high therapeutic requirements.
3	Chemical Instability	Neuroactive compounds may undergo degradation via light, oxygen, or enzymatic activity within the skin, reducing effective delivery.
4	Lipophilicity Challenges	Optimal absorption requires moderate lipophilicity. Excessive hydrophilicity or lipophilicity impairs either skin penetration or release from the patch.
5	Blood–Brain Barrier Considerations	Even after successful dermal penetration, limited BBB permeability of many neuroactive drugs diminishes therapeutic efficacy
6	Dermatological Adverse Effects	Adhesives, active molecules, or penetration enhancers may induce erythema, pruritus, or dermatitis, restricting long-term use.
7	Physiological Variability	Age, hydration status, temperature, and anatomical site influence absorption, resulting in variable pharmacokinetics.

Sr. No.	Impacting Factor	Insight
8	Restricted Candidate Profile	Ideal TDDS drugs must exhibit low daily dose requirements, log P between 1–5, and molecular weight < 500 Da—criteria unmet by many neuroactive agents.
9	Risk of Misuse	CNS-active drugs such as stimulants and opioids pose risks of tampering, dose dumping, or abuse when formulated in patches.

3. CONCLUSION

The transdermal route has been successfully applied to several neuroactive agents, including rotigotine, rivastigmine, selegiline, clonidine, fentanyl (Duragesic), and buprenorphine (Butrans). These formulations demonstrate that sustained modulation of both central and peripheral nervous system activity through transdermal delivery is clinically practical and commercially viable. For instance, rotigotine patches provide continuous dopaminergic stimulation in Parkinson's disease, improving motor performance as well as non-motor symptoms such as sleep disturbances and mood alterations. Rivastigmine patches bypass first-pass metabolism and minimize peak-to-trough fluctuations, thereby enhancing tolerability in patients with Alzheimer's disease. Similarly, transdermal administration of monoamine oxidase inhibitors like selegiline and opioidergic agents such as fentanyl and buprenorphine, achieves effective systemic and CNS drug levels with controlled release, while reducing systemic adverse effects compared with oral formulations. This review article serves as both a clinical evidence map and a molecular design guide. By analysing 41 clinical trials and detailing the physicochemical properties of 21 novel molecules, it provides valuable insights for advancing innovative TDDS. The findings underscore that success in this field depends on aligning drug properties, delivery technologies, and patient needs to achieve safe, effective, and user-friendly neurotherapeutic solutions.

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