Topical Review

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Dopaminergic modulation: revisiting a promising novel pathway for pharmacologic treatment of chronic pain

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1. Introduction

Chronic pain is a major societal burden, causing significant suffering and staggering annual costs.[35] Despite decades of research, available analgesic treatments for chronic pain remain limited[17] with, at most, a moderate therapeutic effect.[17,66] Mechanism-based drug development or personalized therapy is lacking for chronic pain,[69] with pharmacologic treatment still relying mostly on "trial and error" approaches.[80] Mechanism-based drug development can improve the ability to identify effective therapies and enhance efficiency of clinical care.

Pathological changes in the motivational brain circuitry underlying the reward system have recently emerged as a significant contributor to the chronic pain phenotype. Hence, we hypothesize that the reversal of chronic pain is linked to a corresponding reversal in the dysfunction of the reward system.[1,8,20–22,43,58] Research into the neural components of reward in the context of chronic pain has intensified over the past decade, with the goal of discovering more effective, targeted therapeutics for chronic pain and loss of motivation. Here, we present evidence in support of a conceptual framework that links chronic pain and reward processing through the motivational or mesolimbic brain circuitry and how this circuitry might be modulated to improve pain and reward processing in people living with chronic pain (**Fig. 1**).[29] Although the relationship between the pain experience, reward, and other comorbid conditions (eg, depression) intersects in the motivational brain circuitry, an expansive review of these relationships is beyond the scope of this article.

2. The motivational pathway

Motivation is generally defined as an organism's propensity to exert effort to seek rewards or avoid aversive stimuli.[63] The motivational pathway is regulated by the mesolimbic dopaminergic input, centered on the nucleus accumbens (NAc). The NAc receives dense mesolimbic dopaminergic input from the midbrain ventral tegmental area (VTA)[29] and is rich in opioid receptors.[39,56] The NAc is part of the limbic brain[11] and is highly interconnected with the medial prefrontal cortex (mPFC), the amygdala, and hippocampus, and projects to the hypothalamus.[27,29,40] The mPFC receives inputs from the thalamus, amygdala, ventral hippocampus, and agranular anterior insula and is involved in assigning values to behaviorally salient stimuli related to gains, pleasure, loss, or aversion. Together the NAc and mPFC mediate decision making regarding these stimuli.[26,41] It is well-established that the NAc functions as a limbic–motor interface, transforming animal motivations into actions.[28,34,51,62,74]

Peripheral nociceptive input, such as pain from a predator attack, influences motivation through the NAc and mesolimbic circuitry to generate appropriate behavioral responses to protect the animal from harm, such as fleeing. Consequently, it is plausible that pathology in this circuitry could contribute to chronic pain and the associated negative motivational symptoms.[7,65,72] Studies have linked changes in NAc and dopamine signaling to chronic pain[62]; however, the underlying mechanisms causing disruption of dopaminergic transmission in the mesolimbic system associated with chronic pain are not completely clear. This gap may explain why, despite early successes, few randomized clinical trials (RCTs) have investigated the analgesic benefit of dopaminergic compounds, and research in this area has stalled in recent years. Below, we will discuss recent advances in the understanding of the complex disruptions in the mesolimbic pathway in chronic pain and discuss how this understanding could open new avenues for pharmacological research.

3. Preclinical evidence

Studies using different rodent models of chronic pain have shown region-specific alterations in VTA dopaminergic firing,[33,60,61] synaptic connectivity,[60] decreased excitatory postsynaptic potentials of NAc medium spiny neurons,[64] and altered NAc dopamine receptor gene expression.[12] Chemogenetic excitation of the medium spiny neurons of the NAc *shell* indirect pathway worsened mechanical allodynia (ie, a preclinical chronic pain phenotype) whereas inhibition of these neurons alleviated allodynia,[60] suggesting that this pathway is *causally* involved in the neuropathic pain behavior. By contrast, chemogenetic excitation of the medium spiny neurons of the NAc *core* does not alter peripheral allodynia, but does instead lessen the affective phenotype associated with chronic pain such as anxiety and decreased social interaction.[61] Furthermore, the systemic administration of the D2/D3 dopamine receptor agonist

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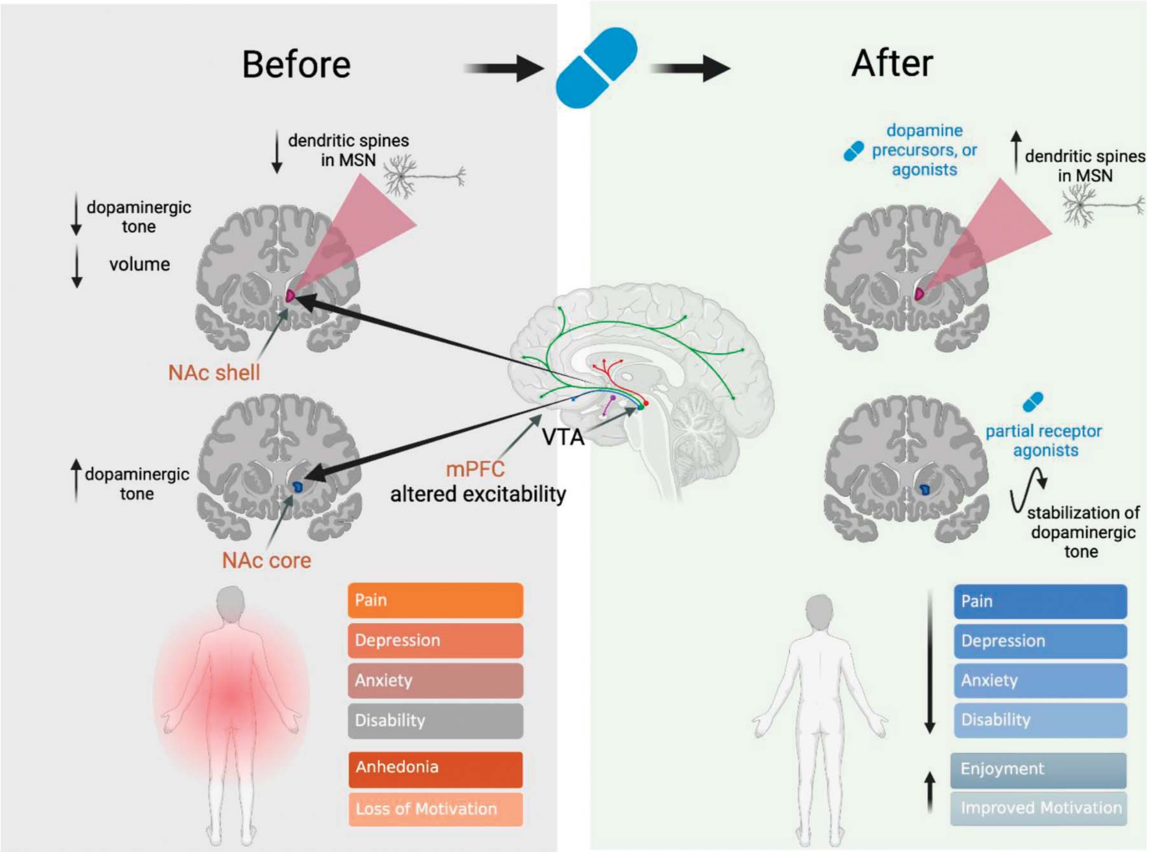

Figure 1. Conceptual framework of motivational brain pathway involvement in chronic pain and the potential role of dopamine modulation in pain therapy.

pramipexole significantly blunted the development of allodynia after neuropathic injury.[60] These results suggest that processing of different aspects of the pain experience along the sensory and affective dimensions is distributed across different NAc pathways and dopamine differential modulation of these pathways might reverse pain behaviors. However, how these observations map onto the distinct roles of the core and shell known from the reward learning literature—namely that the core facilitates the approach while the shell suppresses the devalued or irrelevant behavior—remains to be determined. Both Schwartz et al.[64] and Massaly et al.[50] demonstrated a *causal* role of NAc in mediating pain-related decreases in motivation and increases in negative affect, respectively, in a spared nerve injury rodent model (ie, a model of chronic neuropathic pain). Consistently, targeted and optogenetic modulation of activity of cortico–striatal projections from the prelimbic prefrontal cortex (the equivalent of the mPFC in rodents) to different parts of the NAc relieves[42] or exacerbates chronic pain behavior in rodents.[86] The mPFC also undergoes deactivation in animal models of chronic pain,[37] which when reversed[38,46] can attenuate chronic pain behaviors. The modulation of peripheral nociceptive behavior by the mesolimbic circuitry in rodents suggests that this circuitry is not only involved in mediating the affective dimension of chronic pain but also may be a target in "silencing" peripheral nociceptive input. Taken together, these preclinical data demonstrate that the motivational brain pathway, and thus dopamine-modulated neurotransmission, is directly involved in the sensory and affective perception of chronic pain. The differential involvement of NAc core and shell suggests that a balance of dopaminergic transmission is maintained in pain-free normal conditions and may thus be disrupted in chronic pain states by either too much *or* too little dopaminergic activity.

4. Human genetic studies

A comprehensive review of the genetic evidence supporting the role of altered dopamine transmission in pain is beyond the scope of this article (for review, please see Ref. 87). However, we highlight 2 of the most notable genes. Polymorphisms in the catechol-O-methyltransferase gene, which encodes a key enzyme involved in the metabolism of catecholamines (including dopamine), are consistently associated with chronic pain in many studies.[24,52] Polymorphisms in the dopamine receptor D2 have been linked to temporo–mandibular disorders,[6] migraine,[87] postsurgical pain,[79] and fibromyalgia[10] among others.

5. Human brain imaging–based evidence

Positron emission tomography (PET)–based brain imaging studies directly measure dopamine signaling. Magnetic resonance (MRI)–based brain imaging studies of the activity and structure of the VTA targets in the mesoaccumbal pathway indirectly measure mesolimbic dopamine. Both types of studies support a potential role of dopamine signaling in chronic pain. Positron emission tomography studies reported altered dopamine transmission in the NAc of patients suffering from fibromyalgia,[84] neuropathic,[48] and chronic low-back pain (CLBP).[49] Other PET studies demonstrated such changes in a closely related area to the NAc (ie, the putamen) in patients with facial and burning mouth pains.[30,31] Functional MRI (fMRI) studies have demonstrated that activity in the NAc and mPFC changes with clinical pain fluctuations[2,3,32,47] and long-term analgesic use.[4,23] NAc volume shrinks in different clinical pain populations such as CLBP[5,47] and trigeminal neuralgia.[75] Loss of power in the low-frequency band (0.01-0.027 Hz) of NAc activity is a highly reproducible signature of CLBP.[47] Individuals with subacute back pain who have increased risk of pain chronification (compared with those at low risk of pain chronification) have a smaller NAc volume[5,47] and increased NAc connectivity to the mPFC.[5,44] The consistency and the reproducibility of these findings support the theory that the motivational brain system, which could be treated with dopamine-modulating compounds, plays a role in chronic pain.[1,7,54]

6. Classes of dopamine-modulating compounds

Many clinically available drugs modulate dopamine levels, providing an ideal opportunity to test our proposed hypothesis with the clear advantage of using drugs that have known safety profiles. This approach avoids the risks of investing in new chemical entities that could fail because of toxicity issues, which has contributed to some major setbacks in recent analgesic drug development, including the failure of tanezumab and EMA-401,[68] 2 promising new therapies for chronic pain. In fact, this repurposing strategy supported the development of 2 of the major classes of chronic pain medications developed in the recent history (ie, antiepileptics and antidepressants).

Levodopa is a dopamine prodrug that is converted to dopamine in the brain. Dopamine agonists (eg, pramipexole, ropinirole, and rotigotine) bind and activate dopamine receptors. Dopamine reuptake inhibitors (eg, methylphenidate and bupropion) prevent dopamine reuptake, increasing extracellular dopamine concentration and dopaminergic neurotransmission. Monoamine oxidase-B (MAO-B) inhibitors (eg, selegiline and rasagiline) increase dopamine levels by blocking MAO-B–mediated breakdown of dopamine.

Additional studies suggest that a more nuanced approach than simply increasing dopamine signaling may be required for optimal analgesia. For example, preclinical evidence points to adaptive[61] changes in the NAc *core* and maladaptive[60] changes in the NAc *shell* affecting medium spiny neurons expressing D2-receptors. Evidence also suggests that NAc's D1 and D2 receptors might be involved in separate aspects of chronic pain behavior because a selective antagonist to NAc's D1 receptors changed nociceptive thresholds but not anhedonic behavior in rodents, whereas a selective antagonist to NAc D2 receptors had the opposite effect on these domains.[81] These results imply that different dopamine-modulating drugs may differentially affect the chronic pain (sensory and/or affective) experience because of the complex adaptive and maladaptive patterns arising in the mesolimbic circuitry in chronic pain. Thus, rather than simply increasing dopamine or stimulating dopaminergic receptors, stabilizing dopaminergic transmission across multiple pathways with partial-agonists (eg, aripiprazole)[70] could have optimal analgesic effects. Anecdotal evidence from the literature supports the analgesic efficacy of this approach.[18,71,78] Hence, depending on the chronic pain condition or individual patient, targeting nociception and/or pain through specific dopaminergic pathways may result in differential analgesic efficacy. However, matching conditions to dopaminergic-modulating drugs remains to date a trial-and-error task. Nevertheless, ongoing efforts in brain-based biomarker development[15,85] might advance evidence-based, targeted clinical decision-making.

7. Randomized clinical trials

The analgesic effects of dopamine-modulating drugs have been studied in RCTs, including a dopamine prodrug, dopamine agonists, and dopamine reuptake inhibitors (**Table 1**, **Fig. 2**). The RCTs included highly variable conditions, such as painful diabetic peripheral neuropathy (PDPN), back pain, and fibromyalgia, as well as pain associated with Parkinson disease (PD). A study of levodopa demonstrated efficacy on PDPN (N = 25), while pramipexole (primarily a D2R agonist) improved fibromyalgia pain in another study (N = 60). A cross-over trial of bupropion for neuropathic pain (N = 41) demonstrated analgesic benefit. A study of rotigotine in PD-associated pain (N = 60) reported inconclusive results (ie, the confidence interval of the treatment effect including clinically meaningful differences in pain).[25] One trial of bupropion in nonneuropathic CLBP showed almost identical responses in the placebo and active groups. One study tested the hypothesis that carbidopa/levodopa in combination with naproxen could prevent the transition from acute to chronic low back pain. This study did not detect a treatment effect on the main analysis; however, a small subgroup analysis demonstrated an effect in the female subpopulation.[59] These results require repetition. Overall, these trials suggest that dopamine-modulating compounds are potentially analgesic; however, no studies of sufficient sample size to definitively test the analgesic properties of these compounds have been published. A review of clinicaltrials.gov yields 12 additional clinical trials of dopamine-modulating drugs for pain, suggesting continued scientific interest in this area. However, most of these studies are small and not likely to be sufficiently powered to identify an analgesic signal, suggesting an open space for future research.

8. Where do we go from here?

8.1. Condition

Pain conditions that have prominent nociplastic or centralized features would be a particularly good choice of pain condition because of the increased likelihood of having a dopamine-based mechanistic component in nociplastic pain (eg, patients with chronic overlapping pain conditions [COPC] and fibromyalgia).[19] Not only are these populations theoretically most likely to have an analgesic response to dopamine-modulating compounds but these patients are often the hardest to treat and often have comorbidities that could also benefit from modulation of the motivational brain.[13]

8.2. Drug

If aiming to directly test the hypothesis that dopamine modulation is analgesic, prodrugs and direct dopamine agonists (eg, levodopa and pramipexole) would be best for future clinical trials. However, considering that chronic pain likely has many underlying mechanisms, drugs that act on multiple receptors or neurotransmitters in addition to dopamine may have the best chance of analgesic success. For example, methylphenidate and bupropion inhibit reuptake of serotonin and norepinephrine as well as dopamine, which could improve analgesic efficacy considering multiple efficacious analgesics target these pathways. In fact, efficacious analgesics often act on multiple mechanistic pathways (eg, duloxetine and tramadol). These compounds also have the advantage of affecting multiple domains (eg, mood/cognitive function/fatigue), which are often affected in chronic pain, especially in patients with COPCs.[19] Aripiprazole has an atypical effect on dopaminergic transmission[9,45]; it has high affinity but low efficacy at the D2-receptor. In

Table 1

Summary of published randomized clinical trials that have assessed efficacy of dopamine-modulating compounds to treat or prevent the development of chronic pain.

Article	Treatment/Design	Disorder	Outcome measures	Highlighted results
Dopamine prodrugs				
Ertas et al. (1998)	Levodopa/benserazide parallel group RCT (4 wk) (N = 25)	Painful diabetic polyneuropathy (DPN)	Pain VAS	Pain intensity (VAS) mean at endpoint: Active: 2.5 ± 2 Placebo: 5.7 ± 3 ($P = 0.005$)
*Reckziegel et al. (2021)	Carbidopa/levodopa and naproxen vs placebo and naproxen —- parallel group RCT (24 wk) (N = 61)	Prevention of subacute to chronic low back pain	0-10 numeric rating scale (NRS); Pain Sensitivity Questionnaire, Pain Disability Index, PainDETECT, McGill Pain Questionnaire, Pain Catastrophizing Scale, Pain Anxiety Symptoms Scale, Beck Depression Inventory, Positive and Negative Affect Scale	Responder rate (response defined as at least 20% improvement in pain): Active: 75% Placebo: 78% ($P = 1.0$) Sex by treatment interaction was observed for daily pain intensity ($P = 0.007$), with females exhibiting a mean of 90% pain improvement in the active group vs 37% in the placebo group Sex dependence of Nucleus accumbens/medial prefrontal cortex connectivity at 12 wk after treatment cessation ($P = 0.05$).
Dopamine agonists				
Holman and Myers (2005)	Pramipexole–parallel group RCT (14 wk) (N = 60)	Fibromyalgia	10 cm pain visual analog scale (VAS), fibromyalgia impact questionnaire (FIQ), the Multidimensional Health Assessment Questionnaire (MDHAQ), the pain improvement scale, the tender point score, the 17-question Hamilton Depression Inventory (HAM-d), and the Beck Anxiety Index (BAI).	Pain intensity (VAS) mean change from baseline: Active: −2.48 ± 0.38 Placebo: −0.71 ± 0.54 Between group difference: −1.77 (95% CI: −3.07, −0.47) ($P = 0.008$) FIQ total score mean change from baseline: Active: −3.73 ± 2.79 Placebo: −13.30 ± 2.75 Between group difference: −9.57 (95% CI: −18.01, −1.05) ($P = 0.028$).
Rascol et al. (2016)	Rotigotine transdermal patch—parallel group RCT (13-20 wk) (N = 60)	Chronic Parkinson disease (PD)–associated pain	Change in pain severity (Likert pain scale), King's PD Pain Scale and PD Questionnaire	Pain intensity (11-point Likert scale) mean change from baseline: Active: −2.8 ± 1.84 Placebo: −2.2 ± 2.78 Adjusted mean difference at endpoint (active − placebo): −0.76 (95% CI: −1.87, 0.34) $P = 0.172$
Dopamine reuptake inhibitors				
Semenchuk et al. (2001)	Bupropion SR–crossover RCT (6-wk periods) (N = 41)	Neuropathic pain	Wisconsin Brief Pain Inventory, Patient Global Assessment	Wisconsin brief pain inventory mean at endpoint: Active: 3.99 ± 0.41 Placebo: 5.78 ± 0.32 ($P < 0.001$) Patient global pain relief at endpoint (proportion reporting improved, much-improved, or pain free) Active: 73.2% Placebo: 9.8% ($P < 0.001$)
Katz et al. (2005)	Bupropion crossover-RCT (7-wk periods) (N = 44)	Nonneuropathic chronic low back pain	Pain intensity (0-10 NRS), McGill Pain Questionnaire	Pain intensity NRS mean at endpoint: Active: 3.25 ± 1.93 Placebo: 3.42 ± 1.86 ($P > 0.05$) McGill Pain Questionnaire mean at endpoint: Active: 1.51 ± 0.74 Placebo: 1.65 ± 0.92 ($P > 0.05$)

Different statistics are presented to summarize observed treatment effects based on what was identified as the primary analysis or what was available in the original article.

* Study designed to assess ability of dopamine agonist (combined with anti-inflammatory drug) to prevent chronic pain.

RCT, randomized clinical trial.

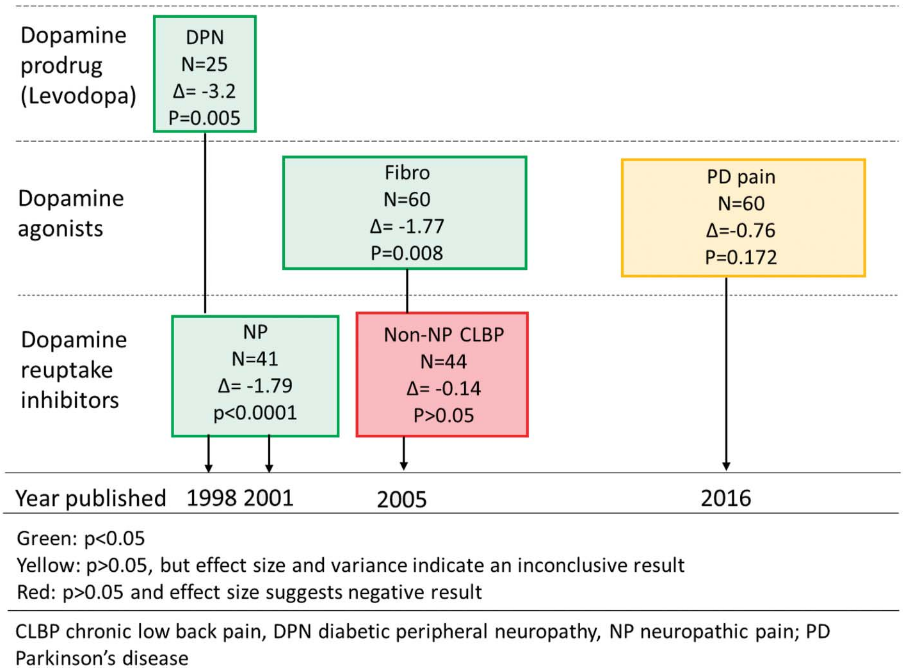

Figure 2. Illustration of published clinical trials examining chronic pain treatment effects of dopamine-modulating compounds.

rodents, under baseline conditions, it acts like a D2-autoreceptor agonist, which inhibits dopamine synthesis. However, under conditions of increased dopaminergic tone, it acts as a D2-autoreceptor antagonist. Germane to the role of NAc in chronic pain, for which dopamine level changes have differential effects on the shell and core, aripiprazole induces differential plasticity in the NAc shell and core.[53] Aripiprazole can therefore act as a dopamine transmission stabilizer.[9] Positron emission tomography studies in humans are consistent with the stabilization hypothesis.[36,67] Interestingly, aripiprazole is also the only drug in its class of antipsychotics that is associated with increased risk of gambling, a risk usually associated with dopamine agonists.[83] Case reports suggest that aripiprazole can improve pain in burning mouth syndrome,[18,71,78] but its analgesic efficacy has yet to be investigated in clinical trials. Cariprazine is a newer antipsychotic medication with partial D2-agonist properties and is believed to also stabilize dopaminergic transmission.[14] Although there are no data on cariprazine's effects on nociception or pain, following the same logic as discussed for aripiprazole, it has potential analgesic efficacy in chronic pain.

8.3. Outcomes

Relevant outcome domains for trials of dopamine-modulating compounds in patients with chronic pain include pain intensity, motivation, anhedonia,[62,73] cognitive function,[57,82] mood,[55] fatigue, and brain structure and function.[16] Benefits on fatigue and impaired cognitive function may be observed when using multimodal treatments with a dopamine-modulating component (eg, methylphenidate and bupropion). These outcomes can be used separately or potentially combined into personalized composite outcomes that include the most important domains experienced by each participant. Trials in acute migraine treatment provide a precedent for such personalized outcomes.[76]

Clinical trials of these medications should be careful to assess their known adverse effects. Expected adverse events include rare seizures (eg, bupropion), abnormal motor symptoms such as akathisia (eg, aripiprazole), weight gain and weight loss (eg, various dopaminergic modulators), serious behavioral adverse events such as drug dependence (eg, stimulants), and pathological gambling (eg, dopamine agonists and partial agonists).

8.4. Master protocols

The use of master protocols would be an ideal option to identify the most promising dopamine-modulating drugs from the multiple candidates to move forward in development. A master protocol is a single protocol that is developed and implemented by the same clinical coordinating center and at the same study sites. This provides efficiencies in developing the protocol, identifying, and training sites, and for regulatory oversight. If possible, a single control group can be shared, further increasing efficiencies.[77] This type of trial would require a collaborative effort and a large amount of funding, but would provide the best chance of identifying the most efficacious analgesics from this promising class.

9. Conclusion

Preclinical and clinical research suggests that dopamine modulation could be an effective analgesic strategy. More research in this area is necessary to identify the most promising compounds in this class and rigorously test their analgesic efficacy in clinical trials.

Conflict of interest statement

This work was supported by grants from the National Institutes of Health (K24NS126861). In the past 36 months, Dr. Gewandter has received grant funding from the National Institutes of Health and funding for contracts with Algo Therapeutics, Averitas Pharma, and Eli Lilly. Dr. Gewandter has received consulting income from Algo Therapeutix, Eikonizo Therapeutics, Eli Lilly, GW Pharma, Hoba Therapeutics, and Vertex. She owns vesting shares in Eisana Corp. She has also received personal compensation for serving as Associate Editor for the Clinical

Journal of Pain. Dr. Freeman has received personal compensation and/or stock options for serving on scientific advisory boards of AlgoTx, Cutaneous NeuroDiagnostics, Glenmark, Glaxo-Smith Kline, Inhibikase, Eli Lilly, Maxona, Novartis, NeuroBo, Osmol, Regenacy, Theravance, and Vertex. He has also received personal compensation for his editorial activities (Editor) with Autonomic Neuroscience–Basic and Clinical.

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