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REVIEW ARTICLE

Naltrexone: A Pan-Addiction Treatment?

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Abstract Addiction is a major public health problem with few efficacious and safe treatments. The goal of this review is to provide an evidence-based assessment of the therapeutic role of the opioid antagonist naltrexone across the addiction spectrum—substance-based and behavioral. The PubMed database was searched for randomized, placebo-controlled clinical trials that investigated the oral or intramuscular long-acting formulation of naltrexone in substance use disorders or behavioral addictions such as pathological gambling, kleptomania, and trichotillomania. Thirty-nine efficacy studies were retrieved, covering alcohol use disorder ($n = 22$), opioid use disorder ($n = 6$), nicotine use disorder ($n = 5$), stimulant use disorder ($n = 2$), gambling disorder ($n = 2$), trichotillomania ($n = 1$), and kleptomania ($n = 1$). Despite the very different presentations within and between both addiction categories, the data, as a whole, show consistency in favor of naltrexone's relative efficacy and safety. Given the potential benefit and good tolerability revealed in the studies, the high morbidity associated with addiction, and the dearth of alternate treatments, naltrexone would seem like an underutilized treatment option. Further, naltrexone's seemingly broad anti-addiction efficacy supports a shared role for brain opioid pathways in the pathophysiology of addiction, broadly defined. More studies investigating the efficacy and tolerability of naltrexone and other opioid modulators are warranted. Studies should also further examine the effect of combining psychotherapy with naltrexone, as well as the potential role of naltrexone in treating comorbid addictions.

Key Points

Naltrexone is a potentially effective and well tolerated treatment in many patients with substance or behavioral addictions.

The naltrexone data support a role for endogenous opioids across the addiction spectrum.

Further research is needed to explore the anti-addiction potential of naltrexone and other opioid system modulators.

1 Introduction

The opiate antagonist naltrexone was first synthesized in 1963 [1]. It is now in use in many countries and has received approval by several regulatory bodies, including the US Food and Drug Administration (FDA) [2], the European Medicines Agency [3], and Australia's Therapeutic Goods Administration [4]. Based on naltrexone's opiate antagonistic properties, clinical trials targeting heroin addiction began in 1973 [5] and led to its approval by the FDA in 1984 [2] for that condition. Since then, based on similarity in clinical presentation and on data implicating the endogenous opioid system in the pathophysiology of other substance use disorders [6–9], naltrexone was tested in the treatment of other drug addictions. As such, data now exist on the use of naltrexone in substance

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addictions beyond opiates, including alcohol use disorder, for which it was approved in the US in 1995 [10], as well as nicotine and stimulant use disorders. More recently, a long-acting formulation delivered intramuscularly every 4 weeks received approval in alcohol dependence (2006) [11] and for the prevention of relapse in opioid dependence (2010) [11], potentially extending the use of naltrexone by helping improve compliance [12].

Meanwhile, phenomenological, neuropsychological and brain imaging research has increasingly highlighted similarities between substance use disorders and behavioral addictions such as pathological gambling [13, 14]. For example, studies point to the presence of similar addiction features, including craving, tolerance, withdrawal, and loss of control [13, 14], which earned them the designation "addiction without a drug" [15, 16]. Indeed, the proposed diagnostic criteria for several behavioral addictions, including gambling disorder, compulsive buying, and problematic Internet use, were partially based on established criteria for substance addiction taken from the third and fourth editions of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM) [17–20]. Neuroimaging, neuropsychological, and opioid pathways research has suggested some biological explanations for these similarities. For example, data from positron emission tomography (PET) and functional magnetic resonance imaging (MRI) studies suggest mesocorticolimbic dopamine dysfunction in both addiction categories [21–23]. Also, neuropsychological data from cognitive and behavioral tasks suggest heightened impulsivity as a shared trait between substance and behavioral addictions [21, 24], and impulsivity, in turn, has been associated with opioid system disruptions [25, 26]. Such data linking behavioral and substance addictions led to the fifth edition of the DSM (DSM-5) reclassification of gambling disorder, arguably the best studied behavioral addiction, under the same category—"Substance-Related and Addictive Disorders"—as established drug addictions [27].

The aim of this paper is to provide an up-to-date review of the role of the opiate antagonist naltrexone in the treatment of addiction—substance-based and behavioral—and to explore how naltrexone's seemingly broad anti-addiction efficacy may support a shared role for brain opioid pathways in the pathophysiology of addiction, broadly defined.

The PubMed database was searched in May 2016 for studies that tested naltrexone in substance use disorders and the most established behavioral addictions. The search combined "naltrexone" with the following terms: "trichotillomania," "skin picking," "gambling," "internet addiction," "compulsive buying," "sex," "opioid," "opiate," "alcohol," "cocaine," "amphetamine," "nicotine," "hallucinogen," and "cannabis." All articles published in English and conducted in human subjects were included, with no restriction on year or country of publication. Restriction was placed on the type of articles retrieved to include only randomized controlled trials (RCTs).

2 Literature Search Findings

The search yielded 856 entries. After elimination of studies that were not placebo-controlled efficacy trials of oral or extended-release intramuscular naltrexone ($n = 778$), studies that tested naltrexone in combination with another pharmacological agent ($n = 17$), studies that compared naltrexone to another experimental intervention ($n = 8$), and studies that targeted multiple psychiatric conditions (e.g., comorbid substance and/or behavioral addictions, addiction comorbid with mood disorder) ($n = 14$), 39 studies remained. They covered alcohol use disorder ($n = 22$), opioid use disorder ($n = 6$), nicotine use disorder ($n = 5$), stimulant use disorder ($n = 2$), gambling disorder ($n = 2$), trichotillomania ($n = 1$), and kleptomania ($n = 1$) (Tables 1, 2, and 3).

To the degree allowed by the literature for each condition, the review will highlight larger, better powered studies, studies with clear inclusion/exclusion criteria, studies with well defined outcome measures, and studies that contributed to regulatory approval.

2.1 Substance Use Disorders

2.1.1 Alcohol Use Disorder

2.1.1.1 Oral Naltrexone Nineteen studies of oral naltrexone in the treatment of alcohol use disorder were retrieved [28–46], with 11 showing some benefit for naltrexone [28–38]. Oral naltrexone 50 mg/day was FDA approved in 1994 for the treatment of alcohol dependence following two single-site RCTs [28, 29]. The first examined the efficacy of naltrexone in 70 male subjects (mean age = 43.4) meeting criteria for alcohol dependence as defined in the DSM, third edition, text revision (DSM-III-R) [28]. The study's objectives included testing naltrexone's efficacy in decreasing alcohol craving, decreasing alcohol drinking, and preventing relapse. Subjects received placebo for 1 week prior to being randomly assigned to 12 weeks of either naltrexone 50 mg/day ($n = 35$) or continued placebo ($n = 35$). All subjects also received standard rehabilitation treatment. Weekly assessments included a breathalyzer test and measures of craving, alcohol consumption, and overall mood.

Results revealed a non-significant difference in compliance rates between the intervention (24 out of 35; 68.6 %) and placebo (21 out of 35; 60 %) groups. Additionally,

Table 1 Placebo-controlled randomized clinical trials of naltrexone efficacy in alcohol addiction

Authors, year	Study design, objective	Sample size (mean age, years)[a]	Primary outcome
Volpicelli et al., 1992 [28]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	70 (43.4), all male	Significantly lower craving scores ($p < 0.01$) and drinking frequency ($p < 0.025$) with naltrexone compared with placebo. No significant difference in compliance rates between naltrexone (68.6 %) and placebo (60 %)
O'Malley et al., 1992 [29]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day with coping skills therapy. Subjects randomized to naltrexone + coping skills, naltrexone + supportive therapy, placebo + coping skills, placebo + supportive therapy	97 (40.5)	Higher abstinence rate with naltrexone + supportive therapy (61 %) compared with naltrexone + coping skills, placebo + coping skills, and placebo + supportive therapy (28, 21, and 19 %, respectively)
Kranzler et al., 2009 [30]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone (targeted administration vs. daily dose; 50 mg/day)	163 (49.1)	Significantly lower average number of drinks per day with targeted naltrexone administration compared with the other groups ($p = 0.014$)
O'Malley et al., 2015 [31]	8-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day in young adults	140 (21.5)	No significant difference in percent days abstinent ($p = 0.39$) or percent heavy drinking days ($p = 0.58$) compared with placebo. Significant reduction ($p = 0.009$) in drinking intensity with naltrexone as measured by total drinks per drinking occasion
Latt et al., 2002 [32]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	107 (45)	Lower relapse rate with naltrexone compared with placebo ($p = 0.042$)
Kranzler et al., 2003 [33]	8-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day on daily or targeted basis	153 (47.3)	Naltrexone was better than placebo in reducing the frequency of heavy drinking during the treatment period
Ahmadi et al., 2009 [34]	36-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	116 (42.97), all male	Higher retention/abstinence with naltrexone compared with placebo ($p = 0.001$)
Morris et al., 2001 [35]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	111	Lower relapse rate with naltrexone compared with placebo ($p < 0.001$)
Guardia et al., 2002 [36]	12-week, double-blind, placebo-controlled RCT testing efficacy, safety and tolerability of oral naltrexone 50 mg/day	202 (42)	Lower relapse rate and better compliance with naltrexone compared with placebo ($p = 0.05$)
Heinälä et al., 2001 [37]	32-week, double-blind, placebo-controlled RCT testing efficacy of oral daily then targeted naltrexone 50 mg/day in combination with coping skills or supportive therapy	116 (45.5)	Lower relapse into heaving drinking in coping/naltrexone group vs. placebo/coping, supportive/naltrexone, and supportive/placebo groups ($p < 0.001$)
Hernandez-Avila et al., 2006 [38]	8-week, double-blind, placebo-controlled RCT testing efficacy of oral targeted naltrexone 50 mg/day	150 (47.3)	Lower alcohol consumption with targeted naltrexone than placebo ($p = 0.002$)
Krystal et al., 2001 [39]	52-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day in combination with counseling	627	No significant differences among long-term naltrexone, short-term naltrexone, or placebo groups in the percentage of days on which drinking occurred and the number of drinks per drinking day
Killeen et al., 2004 [40]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone, 50 mg/day	145 (37.3)	No significant differences between naltrexone, placebo and treatment as usual groups on percent days drinking ($p = 0.32$), drinks per drinking day ($p = 0.21$), average drinks per day ($p = 0.14$), and heavy drinking days ($p = 0.23$)
Knox and Donovan, 1999 [41]	6-month, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	63	No significant difference in craving while in inpatient treatment or in recidivism after treatment between the two groups

Table 1 continued

Authors, year	Study design, objective	Sample size (mean age, years)[a]	Primary outcome
Chick et al., 2000 [42]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	175	No significant difference in intention-to-treat analysis in time to first episode of heavy drinking ($p > 0.05$)
Huang et al., 2005 [43]	14-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	40	No significant difference in relapse rates between the two groups ($p = 0.671$)
Davidson et al., 2004 [44]	10-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	41	Greater reduction in number of drinks per drinking day and percentage of heavy drinking days in placebo vs. naltrexone group at week 10 and week 22 follow-up
Galarza et al., 1997 [45]	4-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone (no dose specified)	20 (55), all male	No significant difference in craving intensity between the two groups ($p = 0.22$)
Gastpar et al., 2002 [46]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	171 (42.7)	No significant differences in time to first heavy drinking episode, time to first drink, mean total number of standard drinks consumed, and number of non-abstinent days
Kranzler et al., 2004 [47]	12-week, double-blind, placebo-controlled RCT testing efficacy and safety of XR-NTX (300 mg initially, then 150 mg/month)	315	Longer time to first heavy drinking day and higher percentage of no heavy drinking with XR-NTX compared with placebo, but not statistically significant ($p = 0.05$)
Garbutt et al., 2005 [48]	6-month, double-blind, placebo-controlled RCT testing efficacy and tolerability of XR-NTX 380 mg/month vs. 190 mg/month	624 (45)	25 % reduction in heavy drinking with XR-NTX 380 mg/month compared with placebo ($p < 0.03$). XR-NTX 190 mg/month resulted in a 17 % reduction ($p < 0.07$) compared with placebo
Kranzler et al., 1998 [49]	12-week, double-blind, placebo-controlled RCT testing efficacy and safety of XR-NTX (206 mg/month)	20	Significantly lower percentage of heavy drinking days with XR-NTX vs. placebo in the injection and follow-up periods ($p = 0.034$ and $p = 0.037$, respectively)

RCT randomized controlled trial, *XR-NTX* extended-release injectable naltrexone

[a] When provided for the entire sample

Table 2 Placebo-controlled randomized clinical trials of naltrexone efficacy in non-alcohol substance addictions

Authors, year	Study design, objective	Sample size (mean age, years)[a]	Primary outcome
Opioid use disorder			
Krupitsky et al., 2004 [50]	6-month, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	52	Significantly more subjects in the naltrexone vs. placebo group remained in the study and did not relapse ($p < 0.05$)
National Research Council Committee on Clinical Evaluation of Narcotic Antagonists, 1978 [51]	8-month, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 100 mg/day alternating with 150 mg/day	192, all males	Efficacy, indicated by the length of time subjects remained in the study, the frequency of positive urine toxicology screens, and craving intensity, tended to support naltrexone
San et al., 1991 [52]	6-month, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 350 mg/week	50	No statistically significant difference in drug consumption or retention
Lerner et al., 1992 [53]	8-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 100 mg/day alternating with 150 mg/day, with 1-year follow-up	31 (26.6)	No significant difference in retention or abstinence during 1-year follow-up between the two groups
Comer et al., 2006 [54]	8-week, double-blind, placebo-controlled RCT testing efficacy of XR-NTX 192 mg/month vs. 384 mg/month	60	XR-NTX 192 mg/month and 384 mg/month were associated with a significantly greater percentage of negative urine toxicology samples compared with placebo ($p < 0.04$ and $p < 0.001$, respectively)
Krupitsky et al., 2011 [55]	24-week, double-blind, placebo-controlled RCT testing efficacy of XR-NTX 380 mg/month	250	Longer abstinence with XR-NTX compared with placebo ($p = 0.0002$). Total abstinence significantly higher with XR-NTX compared with placebo (35.7 vs. 22.6 %, respectively; $p = 0.0224$)
Tobacco-related disorders			
King et al., 2013 [56]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	315	Significant reduction in daily cigarette consumption with naltrexone compared with placebo ($p < 0.05$). Also, significant reduction in smoking urges ($p = 0.02$) and smoking pleasure ($p = 0.07$) with naltrexone
King et al., 2012 [57]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	316	Naltrexone outperformed placebo acutely in prolonging abstinence ($p = 0.057$), delaying time to first cigarette ($p < 0.05$), and reducing the number of cigarettes smoked during active treatment ($p = 0.05$). Benefit not sustained at 26- and 52-week follow-up points
Covey et al., 1999 [58]	4-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50–75 mg/day	68	Higher overall cessation rate with naltrexone vs. placebo ($p < 0.10$)
Wewers et al., 1998 [59]	5-day, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	43	Significant reduction with naltrexone vs. placebo in plasma nicotine levels ($p = 0.005$), number of cigarettes smoked daily ($p = 0.003$), and smoking pleasure ($p = 0.043$)
King et al., 2006 [60]	8-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day	110	No statistically significant difference in quit rates between naltrexone and placebo groups
Stimulant use disorder—cocaine			
Schmitz et al., 2001 [61]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day + relapse prevention (RP) therapy vs. naltrexone + counseling vs. placebo + RP vs. placebo + counseling	85 (34.2)	Lower relapse rate with naltrexone + RP compared with other groups ($p < 0.03$). No significant difference in retention rates among groups

Table 2 continued

Authors, year	Study design, objective	Sample size (mean age, years)[a]	Primary outcome
Stimulant use disorder—amphetamine-type substance			
Jayaram-Lindstrom et al., 2008 [62]	12-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50 mg/day in relapse prevention	80	Higher percentage of negative urine toxicology tests with naltrexone compared with placebo (79.7 vs. 64.1 %; $p < 0.05$). Also, significant correlation between adherence to naltrexone and negative urine toxicology

RCT randomized controlled trial, *XR-NTX* extended-release injectable naltrexone

[a] When provided for the entire sample

naltrexone was associated with statistically significant lower craving scores compared with placebo ($p < 0.01$) and a statistically significant reduction in drinking frequency, as measured by the number of drinking days per week (0.11 vs. 0.57; $p < 0.025$). Although naltrexone did not reduce the frequency of alcohol sampling (defined as consuming at least one alcoholic drink) compared with placebo (46 vs. 57 %, respectively), it was associated with a statistically significant reduction in subsequent drinking once drinking was initiated. Further, naltrexone was associated with a significant reduction in relapse rates compared with placebo (23 vs. 54 %; $p < 0.01$). Finally, naltrexone was relatively well tolerated: only two subjects treated with naltrexone reported significant nausea, and one reported worsening arthritis pain.

A second study [29] tested the efficacy of oral naltrexone in 97 subjects (mean age = 40.5 years) with DSM-III-R-defined alcohol dependence. Subjects, who had abstained from alcohol consumption for 7–30 days prior to study initiation were randomly assigned to 12 weeks of naltrexone 50 mg/day with coping skills training ($n = 29$), naltrexone 50 mg/day with supportive therapy ($n = 23$), placebo with coping skills training ($n = 25$), and placebo with supportive therapy ($n = 27$). Subjects met with a therapist on a weekly basis either to be trained on coping skills, including self-monitoring of drinking behavior, development of cognitive and behavioral strategies, and development of abstinence-oriented leisure activities, or for supportive therapy where only encouragement to abstain from alcohol was provided.

At the end of the 12-week study period, significant differences were identified in abstinence rates: 61 % of subjects receiving naltrexone and supportive therapy maintained abstinence during the study compared with 28 % in the naltrexone and coping skills group, 21 % in the placebo and coping skills group, and 19 % in the placebo and supportive therapy group. The mean time to the first relapse, defined as consuming more than five drinks on one occasion for men and more than four drinks on one occasion for women, also differed: 25 days in the treatment with placebo and coping skills, compared with 35 days in the placebo and supportive therapy group. In contrast, less than half of subjects treated with naltrexone and supportive therapy (34 %) and naltrexone and coping skills (43 %) relapsed by study end. Analysis of subjects who did not abstain ($n = 58$) also revealed significant intergroup variance ($p < 0.04$): less than half of the subjects treated with naltrexone and coping skills relapsed by the end of the 12 weeks, compared with an average time to relapse of 32.5, 25, and 14 days for naltrexone and supportive therapy, placebo and coping skills, and placebo and supportive therapy, respectively. Although naltrexone was well tolerated, three adverse effects occurred more frequently in

Table 3 Placebo-controlled randomized clinical trials of naltrexone efficacy in behavioral addictions

Authors, year	Study design, objective	Sample size (mean age, years)[a]	Primary outcome
Gambling disorder			
Kim et al., 2001 [63]	11-week double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 25–250 mg/day	83	Significant improvement on all three gambling symptom measures with naltrexone: CGI ($p < 0.001$); clinician-rated CGI ($p < 0.001$); and Gambling Symptom Rating Scale ($p < 0.019$)
Grant et al., 2008 [64]	18-week, double-blind, placebo-controlled RCT testing efficacy and safety of three doses of oral naltrexone (50, 100, and 150 mg/day)	77 (36.3)	Greater reduction in PG-YBOCS total score ($p = 0.0094$), gambling urges ($p = 0.0053$), and gambling behaviors ($p = 0.0134$) with naltrexone compared with placebo. Outcomes did not differ significantly among naltrexone doses
Kleptomania			
Grant et al., 2009 [65]	8-week, double-blind, placebo-controlled RCT testing efficacy and safety of oral naltrexone 50–150 mg/day	25 (34.3)	Greater reduction in K-YBOCS total score ($p = 0.001$), stealing urges ($p = 0.032$), and stealing behaviors ($p < 0.001$) with naltrexone compared with placebo. Significant improvement in kleptomania symptom severity (CGI score) with naltrexone compared with placebo ($p < 0.001$)
Trichotillomania			
Grant et al., 2014 [66]	8-week, double-blind, placebo-controlled RCT testing efficacy of oral naltrexone 50–150 mg/day	51 (32.7)	No significant between-group differences ($p = 0.873$) on the MGH-HPS, CGI (Severity and Improvement Scales), HAM-D, HAM-A, or SDS

CGI Clinical Global Impressions, *HAM-A* Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *K-YBOCS* Kleptomania version of the Yale-Brown Obsessive-Compulsive Scale, *MGH-HPS* Massachusetts General Hospital Hair-Pulling Scale, *PG-YBOCS* Pathological Gambling version of the Yale-Brown Obsessive-Compulsive Scale, *RCT* randomized controlled trial, *SDS* Sheehan Disability Scale

[a] When provided for the entire sample

subjects receiving naltrexone when compared with placebo: nausea (32.7 vs. 13.7 %), weight loss (24.5 vs. 7.89 %), and dizziness (34.7 vs. 15.7 %). Other studies have found oral naltrexone to improve various drinking parameters after short-term (8–12 weeks) or longer term (32–36 weeks) administration (Table 1).

Among negative studies in alcohol use disorder (Table 1), a relatively large, long, multi-site trial failed to show an advantage for naltrexone over placebo when added to standardized psychosocial treatment in 627 mostly male veterans with chronic, severe alcohol dependence [39]. Subjects who had been sober for at least 5 days were randomized to 12 months of naltrexone 50 mg/day ($n = 209$; mean age = 49.3); 3 months of naltrexone 50 mg/day, followed by 9 months of placebo ($n = 209$; mean age = 48.5); or 12 months of placebo ($n = 209$; mean age = 49.3). All subjects were offered counseling and programs to enhance compliance. No significant intergroup differences were seen at study end in the percentage of drinking days ($p = 0.31$) or the number of drinks per drinking day ($p = 0.45$). There were no statistical differences between the naltrexone and placebo groups on adverse events reported.

A targeted schedule of administration of naltrexone has also been explored, including in a 12-week RCT conducted in 163 subjects (mean age = 49.1 years) meeting DSM-IV criteria for alcohol dependence [30]. Subjects were randomly assigned to one of four arms: targeted naltrexone 50 mg/dose ($n = 38$); daily naltrexone 50 mg/day ($n = 45$); targeted placebo ($n = 39$); or daily placebo ($n = 41$). Subjects assigned to the daily intervention were given seven tablets of naltrexone 50 mg or matched placebo, and were instructed to take one tablet daily. In contrast, subjects in the targeted groups received five tablets weekly and were encouraged to use at least three tablets weekly by taking one tablet prior to anticipated high-risk drinking (not to exceed one tablet per 24 h).

Targeted naltrexone had a greater effect on the total number of drinks per drinking day compared with the three other groups ($p = 0.014$). Also, although the average number of drinks among women was similar across the study arms, men in the targeted naltrexone group drank less than males in the three other groups ($p = 0.027$) when assessed at study end. In general, nausea and dizziness occurred at a significantly higher rate with naltrexone compared with placebo ($p < 0.0001$ and $p < 0.0007$,

respectively), although no serious adverse events were reported.

More recently, a trial explored efficacy in a subpopulation of young adults [31]. A total of 140 subjects aged 18–25 (mean age = 21.5 years) were randomized to either 8 weeks of naltrexone (25 mg daily + 25 mg targeted) ($n = 70$) or to matched placebo ($n = 70$). Subjects had four or more heavy drinking days (four or more drinks/woman; five or more drinks/man) during the 4 weeks prior to study onset. During the first week of the study, subjects were instructed to take one dose (25 mg) of naltrexone (or matched placebo) on a targeted basis 2 h prior to exposure to drinking situations. As of week 2, all subjects received an additional 25 mg of naltrexone or matched placebo (daily dose). All subjects received an initial 1.5-h session followed by 15- to 20-min motivational therapy sessions every other week. Two primary outcomes, percent days abstinent (PDA) and percent heavy drinking days (PHDD), were assessed using the Brief Young Adult Alcohol Consequences Questionnaire, and liver enzymes were measured at baseline and then monthly.

Compared with placebo, treatment with naltrexone did not result in a significant difference in PDA ($p = 0.39$) or PHDD ($p = 0.58$). Nonetheless, naltrexone was associated with a significant reduction ($p = 0.009$) in drinking intensity as measured by total drinks per drinking occasion. In terms of adverse events, both sleepiness ($p = 0.01$) and headache ($p = 0.06$) occurred more frequently with naltrexone, but there was no significant difference in liver enzyme abnormalities.

2.1.1.2 Extended-Release Naltrexone The non-compliance problem highlighted in some studies of oral naltrexone provided impetus for testing a long-acting depot formulation [12], and the search criteria retrieved three studies, all showing some benefit for the extended-release injectable suspension of naltrexone (XR-NTX) [47–49]. An early RCT [47] assessed the efficacy of an XR-NTX in treating alcohol dependence in 315 subjects who were randomized to receive either XR-NTX ($n = 158$) or placebo ($n = 157$), in addition to five sessions of motivational enhancement therapy. Pulse loading was achieved via two consecutive injections of either XR-NTX (150 mg each) or placebo. Subjects then received monthly injections of either XR-NTX 150 mg or placebo, over a 3-month period. Of the initial 315 subjects, 245 (77.8 %) completed the study. Although no significant difference was seen between groups in time to first "heavy-drinking day" (five or more drinks/day in males and four or more drinks/day in females) ($p = 0.05$), treatment with XR-NTX was significantly superior to placebo on the time to first drinking episode ($p = 0.003$). No significant differences in adverse events were noted between the two groups. Injection site reactions occurred in 5 % of the study sample, with a greater number of subjects in the XR-NTX group reporting one or more injection site reactions ($p = 0.026$).

Another RCT [48] contributed to the FDA approval, in 2006, of XR-NTX 380 mg/month in the treatment of alcohol dependence. The study compared XR-NTX to placebo in 624 subjects (423 males, 201 females; mean age = 45 years) with DSM-IV-defined alcohol dependence and at least two episodes of heavy drinking (five or more standard drinks/day for males, four or more standard drinks/day for females) per week in the 30-day period prior to screening. Subjects received one intramuscular injection every 4 weeks over 24 weeks along with 12 sessions of supportive psychotherapy. Subjects were randomly assigned to one of three interventions: XR-NTX 380 mg/month ($n = 205$), XR-NTX 190 mg/month ($n = 210$), or placebo ($n = 209$).

Compared with the placebo group, subjects receiving 380 mg of XR-NTX experienced a 25 % reduction in heavy drinking ($p < 0.03$), while subjects receiving 190 mg experienced a 17 % reduction ($p < 0.07$). Discontinuation due to adverse drug effects was identically low in the placebo (6.7 %) and 190-mg (6.7 %) groups, but higher (14.1 %) in the 380-mg group. No serious adverse event, including significant liver function abnormality, was reported in any group.

2.1.2 Opioid Use Disorder

2.1.2.1 Oral Naltrexone Compared with alcohol use disorder, our search criteria yielded only four placebo-controlled RCTs testing oral naltrexone in the treatment of opioid use disorder [50–53], with two showing advantage for the medication [50, 51]. In one study conducted in Russia [50], 52 subjects with DSM-IV-defined heroin dependence who had completed detoxification were randomized to 6 months of either naltrexone 50 mg/day ($n = 27$; mean age = 22.8) or placebo ($n = 25$; mean age = 20.7), while undergoing biweekly counseling. Results revealed significant advantages for naltrexone in retention and relapse. Those were noted starting at 1 month and continued throughout the study. At the end of the 6-month study period, 12 of the 27 naltrexone-assigned subjects (44.4 %) remained in the study and had not relapsed compared with four of 25 subjects (16 %) receiving placebo ($p < 0.05$).

Another study [52] tested naltrexone as an adjuvant treatment in 50 subjects aged 18–30 with DSM-III-R-defined heroin dependence. Efficacy measures included the percentage of subjects who relapse into heroin consumption. Following inpatient-initiated, clonidine-based

detoxification, all subjects received oral naltrexone 350 mg/week for 4 weeks. At the beginning of the second month, subjects were then randomized to either naltrexone ($n = 28$) or placebo ($n = 22$) for a 6-month, double-blind treatment period. Results did not reveal naltrexone superiority over placebo in terms of opioid consumption, nor any statistically significant differences in retention rates, drug compliance, or side effects.

2.1.2.2 Extended-Release Naltrexone Two RCTs were retrieved that tested XR-NTX in opioid dependence [54, 55]. One [54] involved 60 subjects aged 19–59 with DSM-IV-defined heroin dependence who were seeking voluntary treatment for heroin dependence. All subjects initially underwent inpatient detoxification, followed by 3 days of oral naltrexone 50 mg/day to test tolerability. Subjects were then randomized for a period of 8 weeks to placebo ($n = 18$), XR-NTX 192 mg/month ($n = 20$), or XR-NTX 384 mg/month ($n = 22$). Efficacy was measured based on the percentage of negative urine toxicology samples during the study (primary outcome).

Both XR-NTX 192-mg/month and 384-mg/month dosages were associated with a significantly greater percentage of negative urine toxicology samples compared with placebo ($p < 0.04$ and $p < 0.001$, respectively). Also, XR-NTX 384 mg/month was associated with a significant increase in days to dropout compared with both placebo ($p < 0.0001$) and XR-NTX 192/month ($p < 0.05$).

XR-NTX 380 mg/month was FDA approved in 2010 for post-detoxification prevention of relapse to opioid dependence following an RCT in 250 subjects (mean age = 29.4 years in the intervention group, 29.7 in the placebo group) [55]. Subjects with DSM-IV-defined opioid dependence had to have completed inpatient detoxification and been opiate-free for >7 days prior to study initiation. Subjects were then randomized to either XR-NTX 380 mg/month ($n = 125$) or placebo ($n = 125$). A total of six injections were administered every 4 weeks over a 24-week period, along with 12 sessions of biweekly individual drug counseling. Abstinence during weeks 5–24 was the primary outcome measure and was assessed via a urine drug test.

Results demonstrated longer abstinence in the XR-NTX group compared with placebo ($p = 0.0002$), as indicated by percentage of opiate-free weeks (90.0 % with XR-NTX vs. 35.0 % with placebo). In addition, total abstinence was significantly higher in the XR-NTX versus placebo groups (35.7 vs. 22.6 %, respectively; $p = 0.0224$). Finally, XR-NTX was well tolerated; the most commonly reported adverse events were nasopharyngitis (7 %), insomnia (6 %), and hypertension, influenza, and injection site pain (each at 5 %).

2.1.3 Tobacco-Related Disorders

Our search retrieved five placebo-controlled RCTs [56–60] that assessed the efficacy of oral naltrexone in the treatment of cigarette smoking, four of which showed some benefit [56–59]. In one study [56], 315 adult subjects were randomly assigned to receive either naltrexone 50 mg/day ($n = 161$) or placebo ($n = 154$). Inclusion criteria specified a smoking pattern of 12–40 cigarettes daily for no less than 2 years and a desire to quit smoking. Subjects were initially (phase 1) administered naltrexone 12.5 mg/day (day 1), 25 mg/day (days 2 and 3), and 50 mg/day (days 4 to 6), or matched placebo. On day 7, all subjects entered a 4-week, open-label phase (phase 2), during which they received one nicotine patch daily and once weekly behavioral counseling, while continuing the same intervention (placebo or naltrexone) from phase 1. The nicotine patch was then withdrawn, and subjects were maintained on naltrexone or placebo alone until the end of week 12 (phase 3). The primary outcome measure was the number of cigarettes smoked daily.

Naltrexone-treated subjects experienced a significant reduction ($p < 0.05$) in daily cigarette consumption compared with placebo (4.21 vs. 2.93 cigarettes less, or a 26 vs. 17 % reduction, respectively). On secondary outcome measures, naltrexone was associated with a significant reduction in smoking urges ($p = 0.02$) and smoking pleasure ($p = 0.07$). Naltrexone was also associated with an increased incidence of nausea, dizziness, and sedation when compared with placebo, most often rated as mild.

Another study [57] assessed smoking quit rates and weight gain in a double-blind, randomized trial that compared oral naltrexone ($n = 162$) with placebo ($n = 154$) in nicotine-dependent subjects with an intent to quit smoking. The study medication was gradually titrated up to 50 mg/day during the week before the quit date and maintained at this dosage for 12 weeks. To attenuate withdrawal symptoms, all subjects received a nicotine patch in the first 4 weeks, along with weekly individual smoking cessation therapy sessions conducted in a cognitive-behavioral mode. Following this period, subjects were maintained on naltrexone or placebo for 12 weeks, with follow-up assessments conducted at 26 and 52 weeks.

At the 12-week assessment point, naltrexone outperformed placebo in quit rates by the prolonged abstinence criteria ($p = 0.057$). It also delayed time to first cigarette (21.0 vs. 15.2 days; $p < 0.05$) and reduced the number of cigarettes smoked during active treatment ($p = 0.05$). However, at the follow-up assessment points after medication discontinuation, the benefit from naltrexone on quit rates was no longer evident: 26 % in both groups at 26 weeks and 17 vs. 23 % in the naltrexone vs. placebo groups, respectively, at 52 weeks.

2.1.4 Stimulant Use Disorder

2.1.4.1 Cocaine Only one placebo-controlled RCT was retrieved that tested naltrexone in the treatment of cocaine use disorder that is independent of other addictions [61]. In that study, 85 subjects (mean age = 34.2 years) with DSM-IV-defined cocaine dependence were randomly assigned for 12 weeks to one of four groups: naltrexone 50 mg/day combined with relapse prevention (RP) therapy ($n = 24$), placebo combined with RP therapy ($n = 22$), naltrexone 50 mg/day combined with drug counseling (DC) therapy ($n = 20$), and placebo combined with DC therapy ($n = 19$). RP therapy was designed to reduce the probability of relapse through improving coping skills in high-risk situations and was based on cognitive-behavioral therapy principles. DC therapy, on the other hand, provided subjects with general information, support, and praise related to abstinence.

All 85 subjects were seen twice weekly for the first 8 weeks then once weekly for a total of 20- to 60-min therapy sessions. Subjects were treated with a daily dose of naltrexone 50 mg or placebo, with 25 mg of riboflavin added to all capsules to monitor compliance via urine analysis. Cocaine use, the primary outcome measure, was assessed through weekly urine toxicology tests, and secondary measures included the Clinical Global Impressions Improvement Scale (CGI-IS).

More than half of subjects (51 %) were lost to follow-up in the first 6 weeks of the study, but there was no significant difference in retention rates among the groups. Intent-to-treat analysis showed that naltrexone combined with RP therapy resulted in less cocaine use over time when compared with the other three groups ($p < 0.03$). Further, subjects treated with RP therapy ($n = 46$) performed better on the CGI-IS compared with subjects treated with DC therapy ($n = 39$) ($p < 0.001$).

Naltrexone-related adverse effects included difficulty sleeping, irritability, and headache (incidence not reported).

2.1.4.2 Amphetamine-Type Substance A 2008 Swedish study [62] compared the effects of oral naltrexone and placebo on relapse rates in 80 subjects with DSM-IV-defined amphetamine dependence and at least 12 days of amphetamine use in the 22 days prior to study initiation. Following a double-blind, randomized design, subjects were enrolled in one of two groups for 12 weeks: naltrexone 50 mg/day ($n = 40$) or placebo ($n = 40$). Adherence was measured via weekly urine analyses of 6-β-naltrexol, the active metabolite of naltrexone.

Compared with placebo, naltrexone was associated with a significantly higher ($p < 0.05$) mean percentage of negative urine samples (79.7 vs. 64.1 %). There was also a significant positive association between adherence to naltrexone and the number of negative urine samples ($p < 0.05$). Naltrexone was generally well tolerated, with 14 subjects in the naltrexone group reporting nausea, headache, fatigue, and gastrointestinal distress.

2.2 Behavioral Addictions

2.2.1 Gambling Disorder

Gambling Disorder is characterized by a recurrent maladaptive pattern of gambling that results in serious impairment in essential spheres of the gambler's life. Two placebo-controlled RCTs [63, 64] have investigated the efficacy of oral naltrexone in the treatment of gambling disorder. The earlier study involved 83 subjects with DSM-IV-defined pathological gambling disorder [63] who received a 1-week, single-blind placebo lead-in followed by randomization to either naltrexone or placebo. The dosage of naltrexone was gradually raised from 25 mg/day until optimal response (based on clinical judgment) or 250 mg/day, whichever occurred first. Adverse effects were assessed weekly, and liver function tests were checked every other week.

Of the 83 subjects, 38 were excluded from the study because of baseline transaminase elevation prior to randomization ($n = 5$), improvement of 50 % or greater during the 1-week placebo lead-in ($n = 22$), loss to follow-up before the sixth visit ($n = 6$), pregnancy during the study ($n = 1$), intolerable side effects ($n = 2$), and inability to keep up with the study schedule ($n = 2$). Consequently, 20 and 25 subjects in the naltrexone and placebo groups, respectively, were included in the final analysis. Compared with placebo, naltrexone was associated with significant improvement on the Gambling Symptom Assessment Scale (G-SAS) ($p = 0.019$), the patient-rated Gambling Symptom CGI ($p < 0.001$), and the clinician-rated Gambling Symptom CGI ($p < 0.001$). Results also suggested significantly more symptom improvement in subjects with more severe baseline G-SAS scores (>4) in both the naltrexone ($n = 17$) and placebo groups ($n = 19$) compared with those with lower baseline G-SAS scores ($p = 0.041$).

Adverse effects were more frequent with naltrexone compared with placebo: nausea (45 vs. 24 %), dry mouth (40 vs. 0 %), drowsiness (35 vs. 20 %), vivid dreams (40 vs. 4 %), diarrhea (20 vs. 8 %), and constipation (20 vs. 8 %). In addition, four subjects developed elevated liver enzymes during weeks 6–8, associated with exposure to 200–250 mg daily naltrexone for 2–3 weeks. Enzyme elevation occurred "almost exclusively" in subjects who were concomitantly treated with nonsteroidal analgesics, and returned to normal within 1–3 weeks following discontinuation of naltrexone. None had subjective symptoms

associated with transaminase elevation. Despite promising results, the final sample size and unequal distribution between study arms limit this study.

A more recent study [64] compared the efficacy of various doses of oral naltrexone to placebo in 77 subjects with DSM-IV-TR-defined pathological gambling who were experiencing at least moderate urges to gamble (a score of >2 on item 1 of the G-SAS), had a score of >5 on the South Oaks Gambling Screen (SOGS), and had gambling behavior within the 2 weeks preceding the study. All subjects received an initial 1-week placebo lead-in, after which they were randomized, for 17 weeks to one of four arms: naltrexone 50 mg/day, naltrexone 100 mg/day, naltrexone 150 mg/day, or placebo. Subjects were assessed using the Structured Clinical Interview for Pathological Gambling (SCI-PG), the G-SAS, the SOGS, and the Pathological Gambling version of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS).

Results failed to demonstrate significant efficacy differences among doses. Comparing all naltrexone-treated subjects ($n = 58$) to placebo ($n = 19$) showed significantly better improvement at study end on the PG-YBOCS ($p = 0.0094$) in naltrexone-treated subjects, with significant improvement starting at week 6 ($p = 0.0002$). Subjects receiving naltrexone also did significantly better on the G-SAS ($p = 0.0162$) and the Sheehan Disability Scale (SDS) ($p = 0.0177$). Most adverse drug effects were classified as mild to moderate by subjects and most commonly occurred during the first week of treatment, with no significant differences in individual adverse effects noted between placebo and naltrexone.

2.2.2 *Kleptomania*

According to the DSM-5 [27], kleptomania is characterized by the recurrent failure to resist impulses related to stealing. The urges are not motivated by a need for the stolen items or their monetary value, and are typically accompanied by a sense of tension prior to the theft episode and pleasure or relief at the time of committing the act. Only one RCT to date [65] has tested the efficacy of naltrexone in treatment of kleptomania. It involved 25 subjects (mean age = 34.3 years) with DSM-IV-defined kleptomania, at least a moderate urge to steal in the week preceding the study, and at least one theft in the 2 weeks preceding the study. Enrolled subjects spent a mean of 47.4 min weekly stealing and 114.3 min weekly struggling with stealing-related urges. Twenty-three (92 %) had been arrested at least once for stealing.

Subjects were randomly assigned to receive either oral naltrexone (titrated from 50 mg/day to a maximum dosage of 150 mg/day) ($n = 12$) or placebo ($n = 13$) for 8 weeks and assessed every 2 weeks using the Yale-Brown Obsessive-Compulsive Scale modified for kleptomania (K-YBOCS). Compared with placebo, naltrexone was associated with a significant reduction in the K-YBOCS score ($p = 0.001$), with significant differences compared with baseline seen by the sixth week of treatment ($p = 0.013$). Differences in remission rates were also significant: eight naltrexone-treated subjects (66.7 %) achieved remission (K-YBOCS score <5), compared with one subject (7.7 %) in the placebo group. Naltrexone was well tolerated, with the most prominent adverse drug effects consisting of nausea, dry mouth, and insomnia, reported by four, one, and one subject treated with naltrexone, respectively.

2.2.3 *Trichotillomania*

Trichotillomania is defined as the recurrent pulling of one's hair that results in hair loss and repeated unsuccessful attempts to decrease or stop the behavior [27]. A placebo-controlled RCT was conducted in 51 subjects (mean age = 32.7 years) with DSM-IV-TR-defined trichotillomania and who experienced urges to pull at least 50 % of the time [66]. Subjects, who spent an average of 84.7 min/day on hair pulling, were randomized to receive either oral naltrexone, gradually increased to 150 mg/day ($n = 25$), or placebo ($n = 26$). Trichotillomania symptom severity (primary outcome) was assessed using the Massachusetts General Hospital Hair-Pulling Scale (MGH-HPS), with secondary measures including the CGI Severity and Improvement Scales, the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D), and the SDS.

Assessment at study end revealed no significant difference between the two groups ($p = 0.873$) as measured by the MGH-HPS, with secondary outcome measures also failing to show benefit for naltrexone.

3 Discussion

A large body of evidence exists to support a role for endogenous opioid pathways in the pathophysiology of addiction. Among substances, the ability of exogenous opioids to act on these pathways may seem obvious, but other addictive substances also appear to exert similar effects. Alcohol causes the release of endogenous opioids, which, by disinhibiting mesolimbic GABAergic neurons, are thought to increase dopamine output [6]. Endogenous opioids may also mediate the reinforcing effects of stimulants such as cocaine, as suggested by animal studies that show reduced cocaine-seeking behaviors when opioid receptor blockers are administered [7, 8]. Further, nicotine increases endogenous opioid neurotransmission by binding to nicotinic acetylcholine receptors on presynaptic neuron

terminals containing opioid peptides, and opioid antagonists attenuate cue-induced nicotine-seeking in rat models [9].

Besides the similarities among substance addictions regarding the role of the opioid system, similarities have been described between the two categories of substance and behavioral addictions. Early research highlighted shared clinical and phenomenological features, which inspired formal definitions of behavioral addictions that were inspired by DSM substance addiction criteria [17, 18]. The biological bases for these similarities may be explained by neuroimaging, neurocognitive, and opioid pathways research. Data from PET and functional MRI studies in both addiction categories suggest mesocorticolimbic dopamine dysfunction that may represent a neural correlate for the disrupted balance between hyperactive subcortical reward systems and hypoactive prefrontal control mechanisms that is hypothesized in addiction [21–23].

Neurocognitive research has yielded valuable data on the role of impulsivity, a trait that has been linked to both substance and behavioral addictions. Indeed, the latter are often referred to as impulse control disorders, and measures of impulsivity via neurocognitive and behavioral tasks suggest similar abnormalities in both addiction categories [21, 24].

The impulsivity that seems to characterize addiction may be caused by disruptions within the opioid system: mouse mu-opioid receptor knockout models show remarkably decreased motor impulsivity [25]; higher mu-opioid receptor availability has been associated with impulsivity [26]; and blunted endogenous opioid release has been documented in pathological gambling [26].

Such evidence for a shared role of the endogenous opioid system in addiction helps explain how naltrexone, an opioid antagonist, may be effective across a rather broad spectrum of addiction. Conversely, naltrexone's positive efficacy data strengthen the argument that endogenous opioids play an important role in addiction.

The relatively large body of efficacy data that suggests possible benefit from naltrexone, the overall lack of well established treatments for substance and behavioral addictions, and the very high morbidity associated with these conditions would suggest that naltrexone is an underutilized pharmacological option in a field without many good alternatives.

Taken together, studies of oral naltrexone indicate that it is generally well tolerated. Although FDA labeling includes a boxed warning regarding hepatocellular injury, these effects tend to be associated with long-term administration of significantly higher dosages than the FDA-approved dosage (e.g., >250 mg/day) and tend to be reversible. Liver chemistry test elevation may also be more likely in patients who are concomitantly taking nonsteroidal anti-inflammatory drugs (NSAIDs) [10, 67], are obese [68], or have dementia [69], although the data are somewhat equivocal and the naltrexone dosages used in the studies that reported these elevations again seem to significantly exceed the FDA-approved dosage of 50 mg/day. Still, naltrexone should be avoided in patients with active liver disease or serum aminotransferase levels that are greater than five times the upper limit of normal [70]. For otherwise healthy patients, a consensus panel convened by the US Substance Abuse and Mental Health Services Administration (SAMHSA) recommends that liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), bilirubin] be conducted before naltrexone initiation and at intervals of 1, 3, and 6 months, followed by yearly testing thereafter [70]. If baseline liver function test results are elevated or there is a history of hepatic disease, the panel recommends that liver function tests be performed more frequently.

Like oral naltrexone, data on the use of XR-NTX also suggest a generally favorable tolerability profile at the FDA-approved dosage of 380 mg/month. A post-hoc analysis [71] of hepatic safety from a 6-month study [47] in 624 subjects with alcohol dependence showed no significant differences in ALT, AST, or bilirubin levels between the XR-NTX 380-mg/month, 190-mg/month, or placebo groups. In addition, GGT was lower in the XR-NTX 380-mg/month group compared with placebo at several points during the study, presumably due to reduced drinking in naltrexone-treated subjects. High (greater than three times the upper limit of normal) liver chemistry tests and hepatic adverse events were infrequent in all study groups (<1 % hepatomegaly in both XR-NTX groups and 0 % in the placebo group; an insignificant difference). Of note, patients who took NSAIDs or were obese showed no increased frequency of high liver chemistry tests or hepatic adverse events. This was also true for patients who drank heavily throughout the study, suggesting no hepatotoxic "synergy" between naltrexone and heavy alcohol consumption.

Unlike other addiction treatments that are opioid agonists or partial agonists and that, because of it, have abuse potential (e.g., buprenorphine and methadone for opioid use disorder), naltrexone is a competitive opioid antagonist with no abuse potential. To the extent that secondary addiction and diversion are growing problems, this can represent a major advantage. However, naltrexone may precipitate withdrawal in patients taking prescription opiate medications or engaging in illicit opioid use. A careful drug history is imperative, and urine toxicological screening is recommended to confirm abstinence from opioids prior to treatment initiation. An opioid-free period of 7–10 days is usually recommended prior to naltrexone

initiation [10]. Transition from buprenorphine or methadone may also precipitate withdrawal and should be approached cautiously [10].

Finally, there are insufficient data to allow specific recommendations on treatment duration, a decision that should be made based on the individual patient's history, treatment response, and the presence of any adverse effects.

Several limitations to this review must be acknowledged. Methodologically, the review is not exhaustive as it covers only one database. As such, some data have not been captured. In addition, the search terms and disorders selected, while generally representative of the most widely recognized addictions, do not cover all possible addictions (e.g., "food addiction"). Further, the review is not systematic; given the large number of disorders covered and the great variability in the degree to which they have been researched, using identical criteria in selecting the studies highlighted in the article would have made the review impossible (very restrictive criteria would have forced us to ignore behavioral addictions; very permissive ones would have yielded a very large number of substance use studies). This challenge is quite unique to this study since prior reviews did not look at a broad range of addictions. Finally, compared with substance use disorders, the number of RCTs conducted in behavioral addictions is small, limiting the conclusions regarding the pathophysiology of addiction as well as the efficacy and, possibly, safety of naltrexone in this group of conditions. Still, despite the shortcomings, no other review has, to our knowledge, taken a comprehensive look at the role of naltrexone across the addiction spectrum, exploring data in both substance and behavioral addictions, and arriving at evidence-based conclusions regarding its role in treating disparate conditions that likely share similar core features.

4 Conclusion

Studies indicate that naltrexone is a potentially effective and well tolerated treatment whose potential benefits may outweigh its risks in many patients struggling with substance or behavioral addiction. The promising research to date justifies further studies into the efficacy and tolerability of naltrexone—alone and in combination with psychotherapy, a cornerstone of any addiction treatment protocol. The naltrexone data strongly suggest a role for endogenous opioids across the addiction spectrum and should prompt exploration of the anti-addiction potential of other opioid system modulators. Finally, given the high rates of comorbidity among disorders of addiction, future investigations should also examine the role of naltrexone in treating polysubstance use, as well as co-occurring substance and behavioral addictions—hardly uncommon clinical and psychosocial challenges.

Compliance with Ethical Standards

Conflict of interest Dr. Aboujaoude and Dr. Salame declare that they have no conflict of interest.

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