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Developmental Considerations for the Use of Naltrexone in Children and Adolescents

Stephani L. Stancil, PhD, APRN; Susan Abdel-Rahman, PharmD; and Jon Wagner, DO

Naltrexone (NTX) is a well-tolerated drug with a wide safety margin and mechanism of action that affords use across a wide variety of indications in adults and children. By antagonizing the opioid reward system, NTX can modulate behaviors that involve compulsivity or impulsivity, such as substance use, obesity, and eating disorders. Evidence regarding the disposition and efficacy of NTX is mainly derived from adult studies of substance use disorders and considerable variability exists. Developmental changes, plausible disease-specific alterations and genetic polymorphisms in NTX disposition, and pharmacodynamic pathways should be taken into consideration when optimizing the use of NTX in the pediatric population. This review highlights the current state of the evidence and gaps in knowledge regarding NTX to facilitate evidence-based pharmacotherapy of mental health conditions, for which few pharmacologic options exist.

ABBREVIATIONS 6βN, 6-β-naltrexol; AKR, aldo-keto-reductase; DOR, δ opioid receptor; FDA, US Food and Drug Administration; KOR, κ opioid receptor; MOR, μ opioid receptor; NTX, naltrexone; UGT, UDP-glucuronosyl transferase; Vd, volume of distribution; WT, wild type

KEYWORDS adolescent; disposition; naltrexone; ontogeny; pediatric; psychopharmacology; substance use

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Introduction

Naltrexone (NTX) is an opioid antagonist initially developed in the 1960s that received FDA approval for treatment of adult opioid addiction in 1984.[1] A decade later, it received approval for adult alcohol use disorder.[1] More recently, NTX has been used for additional conditions across the lifespan, leading to a steady increase in overall use.[2,3] In children and adolescents, NTX is used off-label in the treatment regimen of compulsive and impulsive behavior disorders driven by the opioid reward circuit, such as binge eating, impulsiveness, and non-suicidal self-injury.[4-6] Unfortunately, there remains a paucity of data related to NTX safety and efficacy in children and adolescents to inform optimal pediatric dosing recommendations. These recommendations are ideally based on pediatric-specific data involving the dose-exposure-response relationship necessitating the conduct of prospective studies designed that will generate these data. Absent such data, a thorough review of the NTX disposition and response pathways is necessary to identify where ontogeny and genetic variation may have the largest impact on NTX disposition and response to inform future trial design and dosing recommendations.

Pharmacology

Naltrexone is a synthetic opioid antagonist that has a chemical structure similar to that of oxymorphone, with molecular substitution of cyclopropylmethyl for methyl group. Naltrexone also closely resembles the chemical structure of naloxone, a parenterally administered opioid antagonist, yet NTX is more potent, has increased oral bioavailability, and has a longer half-life.[7] 6-β-naltrexol (6βN) is the primary metabolite (Figure 1) and has 50% to 80% opioid receptor antagonist activity (Table 1). Mechanistically, opioid receptor antagonism prevents activation of the reward pathway (Figure 2) and subsequent dopamine surge responsible for the euphoria associated with opioid administration (e.g., morphine, heroin), pleasure seeking (e.g., food consumption), and compulsive behavior (e.g., gambling, binge eating). Naltrexone can be administered as an oral tablet (Revia, Barr Pharmaceuticals Inc, Pamona, NY) or intramuscular (XR-NTX, Vivitrol, Alkermes Inc, Waltham, MA) injection.[8] Of note, studies in children focus on the use of the oral formulation. Intramuscular injection of a depot formulation of NTX is used to treat opioid and alcohol addiction when daily adherence presents a significant barrier to treatment. Intranasal NTX is currently being investigated as a longer-acting alternative to naloxone for acute opioid overdose.[9,10] Naltrexone has been well tolerated in adult patients without an increase in serious adverse events compared with placebo, despite a wide dosing range.[11-14] Limited data in children related to eating disorders[15] and autism[16-18] additionally demonstrate no serious adverse events. Nausea is the most common side effect (10%–20%), but it is generally relieved with food or slow titration.[15,19,20] Of potential mechanistic concern due to opioid receptor blockade, mood (e.g., anxiety, depres-

Table 1. Opioid Receptor Subtypes and Naltrexone (NTX)–Binding Affinity[45,197-203]

Opioid Receptor	Endogenous Ligand(s)	Primary Effects	NTX Binding Affinity	Relative 6βN Binding Affinity
μ	β-endorphin	Euphoria	Referent (0.0825–1 nM)	35%–50% of NTX (0.74–2.1 nM)
κ	Dysnorphin A and B Neoendorphine	Dysphoria Stress Negative affect	15%–25% of μ (0.509-3.9 nM)	~50% of NTX (2.0–7.4 nM)
δ	Met-enkephalin Leu-enkephalin	Anxiolysis Positive affect	≤1% of μ (8.02–149 nM)	~25% of NTX (29–213 nM)

6βN, 6-β-naltrexol

sion) and sleep disturbances have not been associated with NTX use in adults.[3,21]

Efficacy in Adults

Clinical trials of NTX in adults have focused primarily on opioid and alcohol use disorders (Tables 2 and 3). For these indications, the long-acting intramuscular formulation (XR-NTX) has outperformed the oral tablet in clinical trials, likely because of adherence challenges with daily oral therapy. Beyond opioid and alcohol use disorder, NTX's use in other behavioral disorders has been investigated, and these limited data are summarized in Tables 4 to 7.

Efficacy in Children

Currently, there are no FDA-approved pediatric indications for NTX, yet off-label use occurs in numerous conditions to target symptoms associated with the opioid reward pathway (Tables 8-11). These conditions range from self-harm to disordered eating to non-opioid or non-alcohol addictive behavior. The clinical indications for NTX are vast, with off-label use in many of these pediatric subpopulations increasing. Despite use of NTX across many indications, response rates are variable. When used in autism, a wide range (40%–80%) of patients reported behavioral benefits.[22-25] In adolescents with eating disorders, a little more than 60% demonstrated reduction in binge/purge behaviors.[15] Variable response rates are similar for self-injury based on currently available data. One potential contributing factor to variability in response is variable systemic exposure. Indeed, systemic exposure varies up to 10-fold in adults. Pharmacokinetic data in children do not yet exist. With the number of pediatric patients who could potentially benefit from NTX increasing, we need to understand how developmental and genetic factors may alter NTX disposition, thereby contributing to greater variability in systemic exposure and therapeutic response. In addition, it is important to understand disease-specific alterations in pharmacokinetics and pharmacodynamics that may impact the therapeutic outcome. The following sections will discuss these considerations based on available evidence to date.

Efficacy in Non-behavioral Conditions

Low-dose NTX (typically doses ranging from 10- to 50-fold lower than the FDA-approved oral dose for adult opioid and alcohol use disorder) has been trialed for a wide range of conditions, including chronic pain, inflammatory bowel disease, inflammatory skin disease (e.g., Hailey-Hailey, Sjogren syndrome), and multiple sclerosis in adults,[26-28] and it appears to be safe and well-tolerated. Table 11 lists studies evaluating the efficacy and safety of naltrexone in non-behavioral conditions in children. Low-dose NTX is hypothesized to act like a Toll-like receptor 4 antagonist to alter immune system response and exhibit anti-inflammatory properties.[26,29,30] Prospective, placebo-controlled trials evaluating efficacy are lacking yet are particularly important given high rates of placebo response in pain conditions. Future studies may more clearly elucidate the mechanism of action and efficacy of low-dose NTX.

NTX Disposition

Given the numerous potential indications in the pediatric population, a more comprehensive understanding of NTX's disposition pathway is necessary before widespread adoption occurs in children and adolescents. The following section will discuss the developmental and pharmacogenetic factors that could influence the dose-exposure profile in the pediatric patient, with much of this discussion extrapolated from *in vitro* and existing adult data. The disposition pathway is summarized in Figure 1.

Physicochemical Considerations. The physicochemical properties of NTX are an important determinant of its disposition and pharmacodynamic effects. Naltrexone is a strong base that is highly lipophilic. Naltrexone's octanol to water partition coefficient and distribution coefficient suggest the ability to readily translocate across the cellular membrane and blood-brain barrier,[31,32] thus contributing to an onset of action that is rapid and a duration of action that is prolonged. As a Biopharmaceutics Drug Disposition Classification System Class I drug, high solubility, extensive metabolism, and a minimal role of gut

Table 2. Summary of Naltrexone (NTX) Efficacy and Safety in Adult Trials for Opioid Use

Reference	Sample Size (Study Design)	Drug: Dosing and Duration	Outcomes
Curran[115]	38 (PCT)	NTX: 6 times a wk for 2 mo, then 3 times a wk for 7 mo	No difference in study completion or treatment effects compared with PLB SAE: none
Cornish[116]	51 (PCT)	NTX: 2 times a wk for 6 mo	UDS opioid positive: NTX: 8%; PLB: 30% Probation revoked—return to prison: NTX: 26%; PLB: 56% SAE: none
Hollister[117]	192 (PCT)	NTX: 50 mg/day on Monday–Friday and 100 mg/day on Saturday for 8 wk. Then 100 mg on Monday and Wednesday and 150 mg on Friday for 9 mo	Craving score: NTX: −38.0; PLB: −12.9 UDS opioid positive: NTX: 10%; PLB: 33% SAE: none
Rawson[122]	132 (PCT)	NTX: 50 mg/day for 2 wk, then 50 mg/day on Monday–Friday and 100 mg on Saturday for 6 wk, then 100 mg on Monday and Wednesday and 150 mg on Friday for 16 wk	UDS opioid positive: NTX: 5.9%; PLB: 28% SAE: none
San[124]	50 (PCT)	NTX: 350 mg/wk for up to 1 yr	Treatment completion: NTX: 14.3%; PLB: 36.4% SAE: none
Lerner[118]	31 (PCT)	NTX: 350 mg/wk for 2 mo	Opioid free at 1 yr: NTX: 53%; PLB: 38% SAE: none
Shufman[119]	32 (PCT)	NTX: 25 mg 2 times a wk for 2 wk, then 50 mg 3 times a wk for 10 wk	Opioid free at 12 wk: NTX: 36%; PLB: 19% Treatment completion: NTX: 50%; PLB: 56% SAE: none
Guo[128]	302 (PCT)	NTX: 50 mg/day for 6 mo	Abstinence rate: NTX: 28.6%; PLB: 7.1% SAE: none
Krupitsky[129]	52 (PCT)	NTX: 50 mg/day for 6 mo	Relapse rate: NTX: 30%; PLB: 72% Freedom from relapse at 6 mo: NTX: 44%; PLB: 16% SAE: none
Krupitsky[130]	280 (PCT)	NTX: 50 mg/day for 6 mo, coadministered with FXT	Relapse rate: NTX + FXT: 30%; NTX: 31%; PLB: 60% SAE: none
Stella[131]	56, 4 arms: (PLB, NTX, NTX + PLB, NTX + PZP)	NTX: 50 mg/day ± 10 mg, coadministered PZP for 6 mo	Opioid free at 6 mo: NTX: 43%; NTX + PLB: 43%; NTX + PZM: 86%; PLB: 21% SAE: none
Schottenfeld[132]	126 (PCT)	NTX: 350 mg/wk or BPN up to 84 mg/wk or PLB for 24 wk	Freedom from heroin relapse, days (range): BPN: 79 (61–98); NTX: 64 (44–84); PLB: 39 (25–53) SAE: none
Krupitsky[133]	250 (PCT)	XR-NTX IM: 380 mg monthly for 24 wk	Abstinent rate (range): XR-NTX: 90% (70%–92%); PLB: 35% (11%–64%) SAE: none
Sullivan[134]	60 (ROL)	XR-NTX IM: 380 mg monthly for 24 wk NTX PO: 50 mg/day for 24 wk	Treatment retention rate: XR-NTX: 57%; NTX: 28% SAE: none

BPN, buprenorphine; FXT, fluoxetine; IM, intramuscular; PCT, placebo-controlled trial; PLB, placebo; PO, orally; PZP, prazepam; ROL, randomized, open label; SAE, serious adverse event; UDS, urine drug screen; XR-NTX, naltrexone intramuscular depot injection

Table 3. Summary of Naltrexone (NTX) Efficacy and Safety in Adult Trials for Alcohol Use

Reference	Sample Size (Study Design)	Drug Dosing and Duration	Outcomes
Volpicelli[135]	70 (PCT)	NTX: 50 mg/day for 12 wk	Craving score: NTX: 1.41; PLB: 3.42 SAE: none
Oslin[136]	221 (PCT, genotype controlled for variant rs1799971)	NTX: 50 mg/day for 12 wk	Heavy drinking OR: Wildtype: 0.69 (95% CI: 0.41–1.18); Variant: 1.10 (95% CI: 0.52–2.31) SAE: none
O'Malley[137]	97 (PCT)	NTX: 50 mg/day plus supportive therapy or coping skills therapy for 12 wk	Abstinence rate (supportive group): NTX: 61%; PLB: 19% SAE: none
Anton[138]	1383 (PCT)	NTX: 100 mg/day for 16 wk ± medical management	Days abstinent: NTX: 80% (CV = 33%); PLB: 74% Good clinical outcome (medical management group): NTX: 74%, PLB 58%; NNT: NTX (n = 6) SAE: One possibly related to NTX (not further described)
Garbutt[139]	624 (PCT)	XR-NTX: 190 mg or 380 mg IM monthly for 6 mo	Heavy drinking days (relative to PLB): High dose: −25%; Low dose: −17% SAE: NTX group (eosinophilic pneumonia, interstitial pneumonia)
Kranzler[140]	315 (PCT)	XR-NTX: IM monthly for 3 mo	Absence of heavy drinking: NTX: 23%, PLB: 16% Abstinence rate: NTX: 18%, PLB: 10% SAE: none

CV, coefficient of variation; IM, intramuscular; NNT, numbers needed to treat; PCT, placebo-controlled trial; PLB, placebo; PO, orally; SAE, severe adverse effect

and liver transport-mediated distribution are expected.[33]

Absorption. With NTX predominantly administered orally in children, the extent of systemic exposure is influenced by drug (e.g., physicochemical properties), biologic (e.g., mechanism of intestinal transport), and patient (e.g., pathophysiologic state of the gastrointestinal tract) factors, which can be influenced by development, genetics, and disease.

Naltrexone undergoes rapid and near complete absorption after oral administration.[34,35] This suggests that translocation from the gut lumen to the portal venous circulation occurs via passive diffusion as opposed to transporter-mediated influx and is consistent with predictions based on physiochemical properties.[33] 6βN, a less lipophilic byproduct of NTX resulting from hepatic reduction by cytosolic aldo-keto reductases,[36] could theoretically be subject to transporter-mediated reabsorption during enterohepatic recycling. However, there is currently a paucity of data related the degree of 6βN recirculation or its affinity for transporter-mediated translocation. Given 6βN's contribution to opioid antagonism, its candidacy for transporter-mediated cellular translocation (in both intestine and brain) must be investigated as a potential additional source of variability in NTX response.

Despite nearly complete absorption, the absolute bioavailability of NTX is low (~5%–40%) because of a high hepatic extraction ratio and extensive first-pass metabolism.[34,35] Naltrexone is not a substrate for enterocyte efflux transporters, such as P-glycoprotein, breast cancer resistance protein, or multidrug resistance–associated protein (MDR2), known to attenuate absorption.[37-39] Developmental and genetic factors may contribute to variability in bioavailability through their impact on metabolizing enzymes responsible for first-past metabolism.

Oral absorption of NTX may be impacted by the baseline physiologic state or pathophysiologic state it is treating. For example, delayed gastric emptying and total gut transit time, known to reduce drug absorption,[40] occur in patients with eating disorders.[41] Yet, the impact of these gastrointestinal alterations on NTX absorption has not yet been investigated in an eating disorder population. An altered microbiome associated with anorexia nervosa, obesity, and autism spectrum disorder[42-44] may affect the extent of enterohepatic recycling. It is unclear whether microbiome alterations lead to clinically meaningful changes in systemic exposure because no pharmacokinetic data in this patient population are available.

Distribution. Naltrexone is widely distributed throughout the body, as evidenced by an average volume of distribution (Vd; ~1350 L) that greatly exceeds intravascular volume and total body water stores.[1] Based on the physicochemical properties of NTX, hepatic uptake and peripheral tissue distribution likely occur by pas-

Table 4. Summary of Naltrexone (NTX) Efficacy and Safety in Adult Trials for Obesity and Eating Disorders

Reference	Sample Size (Study Design)	Drug: Dosing and Duration	Outcomes
Overweight and/or obesity			
Apovian[141]	1496 (PCT)	NTX: 32 mg/day + bupropion 360 mg/day up to 56 wk	Weight: NB: −6.4%, PLB: −1.2% 5% weight loss: NB: 50.5% (CV = 124%); PLB: 17.1% SAE: NB: 2.1% (1 myocardial infarction, 1 seizure), PLB: 1.4%
Kolotkin[142]	3362 (PCT)	NTX: 32 mg/day + bupropion 360 mg/day for 56 wk	Weight: NB: −7.0% (CV = 129%); PLB: −2.3% Weight-loss associated QoL score: NB: +11.9, PLB: +8.2 SAE: none
Hollander[143]	505 (PCT)	Overweight/obese with type 2 diabetes. NTX: 32 mg/day + bupropion 360 mg/day for 56 wk	Weight: NB: −5.0% (CV = 98%), PLB: −1.8% 5% weight loss: NB: 44.5%; PLB: 18.9% SAE: 3.9% NB vs 4.7% PLB (similar profile to non-diabetic patients)
Wadden[144]	793 (PCT)	NTX: 32 mg/day + bupropion 360 mg/day for 56 wk + behavioral modification	Weight: NB: −9.3% (CV 94%), PLB: −5.1% 5% weight loss: NB: 66.4%, PLB: 42.5% (CV = 94%) SAE: none
Greenway[145]	1742 (PCT)	NTX: 16 or 32 mg/day + bupropion 360 mg/day for 56 wk	Weight: NB16: −4.9% (CV = 133%); NB32: −6.1% (CV = 107%); PLB: −1.4% 5% weight loss: NB16: 39%; NB32: 48%; PLB: 16% (CV = 133%) SAE: none
Malcolm[151]	N = 41 (PCT)	Obesity – NTX: 200 mg/day × 8 wk	Weight loss, kg: NTX: 1.8 (CV = 200%), PLB: 1.5 Female: NTX 1.5, PLB 1.5 Male: NTX: 2.6, PLB: 1.4 SAE: NTX: 3 patients had liver transaminases 2 × ULN
Mason[152]	N = 44 (PCT with crossover)	Obese females – Day 1: PLB; Day 4: NTX 25 mg; Day 7: PLB; Day 10: NTX 50 mg; Day 38: NTX 50 mg	NTX blunted association between reward-based eating drive and food craving (50 mg vs PLB) SAE: none
Eating disorders			
Mitchell[146]	16 (PCT with crossover)	BN with normal weight – NTX: 50 mg/day for 3 wk	Binge days/wk: NTX: 4.9 (CV = 106%); PLB: 5.7 Vomit days/wk: NTX: 7.0 (CV = 143%), PLB: 7.6 SAE: none
Alger[147]	Obese BED: 4; NL weight BN: 28 (PCT)	NTX: Titrate up to 50 mg thrice daily for 6 wk	Bingeing: Obese BED: −70% (SIQR: 21.4%) BN: −30% (SIQR: 15.6%) SAE: none
Marrazzi[148]	N = 19 (PCT with crossover)	AN and BN – NTX: 100 mg twice daily for 6 wk	Binge and purge symptoms: Reduction in 95% of participants SAE: none
Jonas[149]	N = 10 (open-label)	Antidepressant-resistant BN – NTX: 300 mg/day for 6 wk	Bulimic symptoms: Reduction of ≥75% in 70% of participants SAE: none
Jonas[150]	N = 16 (Open-label, randomized dosing scheme)	BN – NTX: ≤100 mg/day vs ≥200 mg/day for 6 wk	Binge days: High dose: −5.1 (CV = 150%); low dose: −1.9 (CV = 35%) Purge days: High dose: −3.9; low dose: −1.5 SAE: none

AN, anorexia nervosa; BED, binge eating disorder; BN, bulimia nervosa; CV, coefficient of variation; NB, NTX/bupropion; NB16, NB + 16 mg of NTX; NB32, NB + 32 mg of NTX; NL, normal PCT, placebo-controlled trial; QoL, quality of life; SIQR, semi-interquartile range; ULN, upper limits of normal

Table 5. Summary of Naltrexone (NTX) Efficacy and Safety in Adult Trials for Self-injurious Behavior (SIB)

Reference	Sample Size (Study Design)	Disease: Dosing and Duration	Outcomes
Sandman[153]	24 (randomized)	SIB – NTX: 0.5, 1, and 2 mg/kg	SIB: – >50% in >50% participants SAE: none
Sonne[154]	5 (open-label)	Females with borderline personality disorder – Wk 1: baseline; Wk 2: NTX 50–100 mg/day; Wk 3: post-NTX	YBOCS (modified for SIB): −48% (CV = 48%) SAE: none
Willemsen-Swinkels[155]	33 (PCT with crossover)	Adolescents and adults with intellectual disability – NTX: Titrate up to 150 mg/day for 4 wk	Stereotypic behavior: autistic +3% (CV = 47%); non-autistic +35% (37%) Global function: 50 mg +28%; 150 mg +21% SAE: none
Sandman[156]	4 (DB, PCT with crossover)	Males – NTX: 0, 25, 50, 100 mg twice weekly for 4 wk	SIB: −50%; No SIB at 100 mg in 75% SAE: none
Kars[157]	6 (PCT with crossover)	Males with intellectual disability – NTX: 50 mg/day for 3 wk	SIB: 40% experienced reduction SAE: none
Symons[158]	4 PCT with crossover)	Adults with intellectual disability – NTX: 1.5 mg/kg for 2 wk	SIB: reduction of ≥33% in 75% of participants SAE: none
Roth[159]	7 (open-label)	Females with SIB – NTX: 50 mg/day	SIB: cessation in 85% of participants SAE: none
Zingarelli[160]	8 (PCT with crossover)	Adults with autism – NTX: 50 mg/day for 3 wk	SIB: +22% over baseline SAE: none
Symons[161]	4 (PCT with crossover)	Adult males with intellectual disability – NTX: 1.5 mg/kg/day for 10 wk	SIB: −33% to −54% SAE: none
Thompson[162]	8 (PCT with crossover)	Adults with intellectual disability – NTX: 50 mg/day and 100 mg/day x for wk	Head-banging: 67%–77% of participants had reduction Self-biting: 100% of participants had reduction SAE: none
Sandman[109]	31 (PCT with crossover)	Adults with intellectual disability – NTX: 0.5, 1.0, 2.0 mg/kg/wk	SIB: participants experiencing ≥25% reduction: 0.5 mg/kg: 47.4% ≥1 mg/kg: 52.6% SAE: none

PCT, placebo-controlled trial; PLB, placebo; SAE, serious adverse event; SIB, self-injurious behavior; YBOCS, Yale-Brown Obsessive Compulsive Scale

sive diffusion. Naltrexone easily passes the blood-brain barrier with a partition coefficient that exceeds that of morphine[31] and evidence of μ receptor (MOR) occupancy in the human brain by <8 hours after a single oral dose and persisting for >48 hours.[11,45] Substantial interindividual variability in NTX Vd has been demonstrated and may be partially explained by its lipophilic properties. Although conventional wisdom assumes that highly lipophilic drugs are more widely sequestered in conditions of relative high body fat (e.g., obesity), no consistent relationship between Vd and body fat percentage has been appreciated. This may be due in part to sequestering of the drug in body fat with unpredictable release back into the plasma, leading to an inconsistent alteration in systemic exposure.[46] Developmental changes in total body fat relative to total body water may contribute to variability in NTX distribution in young children. The total body water to fat ratio is much higher in infants and normalizes around 2 to 3 years of age.[47,48] It remains unclear whether the gradual increase in total body fat as a result of development leads to a correlative increase in NTX Vd. Disease-specific changes in total body fat may be dynamic (e.g., anorexia nervosa) and compound the challenges of understanding the relationship between total body fat and Vd. Low body fat seen in acute anorexia nervosa resolves with weight restoration and may contribute to intervariability and intravariability in the Vd[49-51]; however, the influence of disease state on NTX Vd in children and adolescents remains unknown. The impact of total body weight on the Vd is also not

Table 6. Summary of Naltrexone (NTX) Efficacy and Safety in Adult Trials for Pruritis

Reference	Sample Size (Study Design)	Disease: Dosing and Duration	Outcomes
Wolfhagen[163]	16 (PCT)	Chronic cholestatic pruritis – NTX: 50 mg/day for 4 wk	Day itching (VAS): NTX: −54% (range, <5–55); PLB: −8% Night itching (VAS): NTX: −44% (range, <5–50); PLB: −7% SAE: none
Mansour-Ghanaei[164]	34 (PCT)	Cholestatic pruritis – NTX: 50 mg/day for 1 wk	Day pruritis (VAS): NTX: 7.54 (CV = 52%); PLB: 4.91 Night pruritis (VAS): NTX: 8.29 (CV = 45%); PLB: 5.54 SAE: none
Peer[165]	15 (PCT with crossover)	Uremic hemodialysis patients – NTX: 50 mg/day for 7 days	Pruritis (VAS): Baseline: 9.9; NTX: 2.1 (IQR: 1.5–2.15) SAE: none
Pauli-Magnus[166]	23 (PCT with crossover)	Uremic hemodialysis and peritoneal dialysis – NTX: 50 mg/day for 4 wk	Pruritis (VAS): NTX: −29.2% (95% CI: 18.7–39.6); PLB: −16.9% SAE: none
Malekzad[167]	38 (PCT)	Atopic dermatitis – NTX: 50 mg/day for 2 wk	Pruritis (VAS): NTX: 1.3 (CV = 107%); PLB: 4.5 Remission: NTX: n = 6; PLB: n = 0 SAE: none
Legroux-Crespel[168]	52 (RCT)	Uremic hemodialysis – NTX: 50 mg/day for 2 wk; LOR: 10 mg/day for 2 wk	Pruritis score: NTX: 27% of NTX patients had reduction with >3 VAS points SAE: none
Terg[169]	20 (PCT with crossover)	Cholestatic pruritis – NTX: 50 mg/day for 2 wk	Day pruritis (VAS): NTX: −56% (CV = 67%) Night pruritis: NTX: −40% (CV = 68%) Pruritus score: 45% of patients had >50% decrease SAE: none
Ajayi[170]	12 (RCT)	Chloroquine-induced pruritis – NTX: 50 mg pretreatment for 1 dose; PMZ: 25 mg pretreatment for 1 dose	Parasitic pruritogenic index: NTX: 9.1 (CV = 69%), PMZ: 12.1 SAE: none

CV, coefficient of variation; LOR, loratadine; PCB, placebo; PCT, placebo-controlled trial; PMZ, promethazine; RCT, randomized controlled trial; SAE, serious adverse event; VAS, visual analog scale

well understood, but some insight may be gleaned from studies of structurally similar compounds (e.g., morphine). A study of intravenous morphine administered to morbidly obese adults and healthy-weight controls demonstrated that obesity was associated with variability in morphine Vd but did not impact systemic exposure or elimination.[52] Collectively, many drug and patient factors could alter Vd, but it is unclear if this variability in exposure impacts the NTX response at the level of the individual pediatric patient.

With minimal protein binding of NTX (~20%),[1,11] age- and disease-related changes in plasma proteins (e.g., albumin, α-1-acid glycoprotein) and/or binding affinity are not expected to have a meaningful impact on the observed variability in disposition and systemic exposure. Plasma proteins increase in the quantity and binding affinity after birth, approaching adult levels within 6 months to 3 years of life.[53-55] The impact of pediatric disease states on plasma protein concentration is controversial. For example, in anorexia nervosa, systemic albumin-binding and sex hormone–binding globulin concentrations were not significantly different compared with healthy controls.[56,57] However, albumin was notably reduced in a subset of anorexia nervosa patients with the lowest body mass index, suggesting there is a threshold at which albumin declines. In a study of hospitalized pediatric patients, approximately 10% had moderate to severe protein-energy imbalance, and a quarter of patients had serum albumin levels <30 g/L.[58] Although changes in plasma proteins are not likely to affect NTX distribution, the protein-binding affinity of the active metabolite, 6βN, is unknown and requires further elucidation.

Metabolism. Naltrexone undergoes extensive biotransformation into the major metabolite 6βN and the minor metabolites 2-hydroxy-3-*O*-methyl-6-β-naltrexol and 3-*O*-methyl-6-β-naltrexol, 2-hydroxy-3-methyl-naltrexone.[1,59-61] Conjugated forms of NTX and metabolites are also observed and exceed the concentration of unconjugated NTX in plasma and urine.[35,59]

First-pass metabolism after oral administration leads to reduced bioavailability of 5% to 40% of the parent drug. The maximum plasma concentration of NTX is highly variable (~10-fold) in adults.[13,34,62] Plasma concentrations of the primary metabolite, 6βN, exceed that of the parent by approximately 10- to 40-fold, with less variability

Table 7. Summary of Naltrexone (NTX) Efficacy and Safety in Adult Trials for Gambling and Other Behavioral Disorders

Reference	Sample Size (Study Design)	Disease: Dosing and Duration	Outcomes
Ward[171]	14 (case series)	"Problem gamblers" – NTX: 50 mg/day	Gambling behavior/urge: − ≥83% SAE: none
Bosco[172]	3 (case series)	Pathologic gambling in Parkinson disease – NTX: 50 mg/day for 6–8 mo	Remission of pathologic gambling: 100% SAE: none
Grant[173]	25 (PCT)	Kleptomania – NTX: Titrate up to 150 mg/day for 8 wk	K-YBOCS: NTX: 3.83 (CV = 75%); PLB: 11.46 SAE: none
Grant[174]	77 (PCT)	Pathologic gambling – NTX: Up to 150 mg/day for 18 wk	PG-YBOCS: NTX: 9.7 (CV = 84%); PLB: 12.9 Abstinent at 1 mo: NTX: 40%; PLB: 11% SAE: none
Kovanen[175]	101 (PCT)	Pathologic gambling – NTX: 50 mg as needed (advised to take if urge to gamble or 30–60 min prior to gambling) for 20 wk	PG-YBOCS: NTX: 10.3 (CV = 74%); PLB: 13.1 SAE: none
Papay[176]	50 (PCT)	Impulsive compulsive disorder in Parkinson disease – NTX: 50–100 mg/day for 8 wk	QUIP-RS ICD Δ: NTX: −14.9 (95% CI: −9.9 to −19.9); PLB, −7.5 SAE: none
Grant[177]	51 (PCT)	Trichotillomania – NTX: up to 150 mg/day for 8 wk	MGH-PHS score: NTX: 12.2 (CV = 51%); PLB: 13.6 SAE: none
Toneatto[178]	52 (PCT)	Alcohol abusing and pathologic gambling – NTX: up to 250 mg/day for 11 wk (following 1-wk placebo run-in)	Gambling frequency: NTX: 11.4 (CV = 101%); PLB: 10.8 SAE: none

CV, coefficient of variation; K-YBOCS, Yale-Brown Obsessive Compulsive Scale adapted for Kleptomania; MGH-PHS score, Massachusetts General Hospital Hair-Pulling Scale; PCT, placebo-controlled trial; PG-YBOCS, Yale-Brown Obsessive Compulsive Scale adapted for Pathological Gambling; PLB, placebo; QUIP-RS ICD: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; SAE, serious adverse event

demonstrated (~4-fold).[63] When NTX is administered in an intramuscular depot formulation (thus bypassing first-pass metabolism), 6βN levels more closely approach the parent,[13] suggesting a significant impact of first pass on 6βN formation.

6βN is formed through hepatic metabolism. *In vitro*, 6βN formation was restricted to the cytosol and was not detected in the liver microsomal fraction, suggesting no contribution from cytochrome p450.[36] Naltrexone use in heroin addicts did not affect antipyrine metabolism, a non-specific probe of CYP450 enzymes, compared with baseline and healthy controls.[64] The ability of NTX to affect medications metabolized through specific CYP450 enzymes has been investigated *in vitro*. Evidence suggests that NTX may have a modest inhibitory effect (~30%) on CYP2C9, CYP2D6, and CYP3A4, and no effect on CYP1A2.[65] CYP2D6 and CYP2C19 are involved in the metabolism of many psychiatric medications, such as selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and antipsychotics, that may be taken concomitantly with NTX and are not likely to affect NTX metabolism, but these effects have not been investigated in human trials.

In the presence of the ketone reductase inhibitor menadione, 6βN formation was greatly diminished.[66] Further analysis identified the aldo-keto reductase 1C (AKR1C) family, specifically AKR1C4, as the major enzyme responsible for 6βN formation, followed by minor contributions from AKR1C1 and AKR1C2.[67,68]

The AKR1C family is a group of cytosolic enzymes, formerly known as dihydrodiol dehydrogenases, also involved in endogenous steroid biotransformation (e.g., testosterone). AKR1C4 is liver specific, whereas AKR1C2 and AKR1C1 are found in other tissues, including the brain and reproductive organs.[69,70] Developmental alterations in this metabolic pathway may contribute to variability in exposure in children and adolescents; however, the ontogenic pattern of AKR1C enzymes in humans is currently unknown. The utility of ontogenic data from animal studies is limited by increased plasticity and catalytic activity in the single-isoform AKR1C9 compared with individual human AKR1C isoforms.[71] Although murine AKR1C9 was found to have activity in fetal rat osteoblasts, it is difficult to interpret the human relevance.[72] Although exceedingly variable among adult patients (128-fold), stable 6βN/NTX ratios in urine over time ar-

Table 8. Summary of Naltrexone (NTX) Efficacy and Safety in Pediatric Trials Involving Substance and Sexual Addiction.

Reference	Sample Size (Study Design)	Dosing and Duration	Outcome
Miranda[179]	22 (PCT with crossover)	15- to 19-yr–old adolescents with problem drinking – NTX: 50 mg/day for 8–10 days	Drinking days: NTX: 2.4 (CV = 58%); PLB: 3.1 Heavy drinking days: NTX: 1.1 (CV = 90%); PLB: 1.6 SAE: none
Deas[19]	5 (open-label)	Treatment-seeking adolescents with alcohol dependence – NTX: 50 mg/day up to 6 wk	Drinks per drinking days compared with baseline: −7.61 (CV = 13%) SAE: none
Hulse[180]	8 (retrospective case series)	15- to 19-yr–old opioid dependent – NTX: 50 mg/day oral followed by NTX implant	Opioid overdose/yr: Implant: 0.19 (SE = 0.13); Oral: 1.9 (SE = 0.74) Baseline: 8.9 SAE: none
Fishman[181]	16 (Retrospective case series)	Opioid-dependent adolescents and young adults – NTX: implant	Retained in treatment ≥4 mo: 63% "good" outcome defined as substantially decreased opioid use: 56% SAE: none
Ryback[183]	21 (open-label)	13- to 17-yr adolescents with sexual addiction – NTX: up to 200 mg/day for an average of 12 months (range 4.5-21 months)	Responders: 71% Relapse: occurred in n=13 when NTX tapered ≤50 mg/day

CV, coefficient of variation; PCT, placebo-controlled trial; PLB, placebo; SAE, serious adverse event

gue against autoinduction of metabolism.[11,36,73] Liver X Receptor (LXRα), a nuclear receptor activated by bile acid metabolites, induces *AKR1C4* gene expression.[74] AKR1C enzymes are inhibited by sex hormones (e.g., testosterone), although it is unlikely that any clinically relevant inhibition exists given the high concentrations required to achieve an effect (e.g., >10-fold higher than the upper limit of normal in males).[36] This suggests against a sex hormone–dependent effect on NTX metabolism.[75] After oral administration, no sex-related difference in NTX clearance has been observed.[13] In a small study in healthy adults receiving long-acting intramuscular NTX, the maximum plasma concentrations of both NTX and 6βN were 30% lower in females, whereas area under the curve ranged from 15% lower to 30% higher compared with males. Sex differences in muscle capillary density have not been appreciated.[76] The mechanism responsible for possible reduced exposure XR-NTX in females remains unclear. Of note, sex differences in children, particularly comparing those that are prepubertal vs postpubertal, have not been explored.

The impact of AKR1C genetic variability on NTX variability is largely unknown. Two single-nucleotide polymorphisms (rs17134592 and rs3829125) leading to the missense mutations L311V and S145C, in AKR1C4 show decreased catalytic activity toward NTX when expressed in recombinant enzymes *in vitro*.[77] L311V and S145C mutations are fairly common in the population sharing the mean allele frequencies of 10% to 51%.[78,79] It remains unclear whether polymorphisms impact NTX biotransformation *in vivo*, but this merits further elucidation.

Phase II UDP-glucuronosyl transferase (UGT)–catalyzed conjugation is the mechanism by which the water solubility of NTX and 6βN is increased to enhance renal elimination.[80,81] UGT2B7 appears to be the predominant isoform responsible for NTX and 6βN glucuronidation, with minor contributions from UGT1A1 and UGT2B1.[80,82,83] The ontogenic pattern of UGT2B7 has been characterized using the probe substrates morphine[84] and naloxone, a structurally similar oxymorphone analogue,[85] where drug clearance is diminished in neonates compared with adults. Expression of UGT2B7 in pediatric liver tissue appears to be age dependent. There is a rapid increase in expression through infancy into young childhood, achieving 50% abundance of adult levels at approximately 3 years of age.[86] Expression is not significantly different in early childhood through adolescence, but there is a 2.5-fold increase in activity in adults compared with adolescents.[86] It remains unknown whether the ontogeny of UGT2B7 significantly affects the disposition of NTX clinically; however, application of ontogeny to morphine physiologically based pharmacokinetic models to children older than 1 year did not significantly alter morphine exposure prediction, suggestive of minimal changes to UGT2B7 expression in children ages 1 to 18 years.[86] Commonly occurring genetic variants in UGT2B7 have not demonstrated a significant impact on protein abundance or activity *in vitro*.[86] Genotype-informed *in vivo* studies that use specific UGT2B7 probe substrates will be needed to determine whether meaningful differences in activity exist.

Body weight–related changes on UGT2B7 activity

Table 9. Summary of Naltrexone (NTX) Efficacy and Safety in Pediatric Trials in Self-injury and Autism

Reference	Sample Size (Study Design)	Dosing and Duration	Outcome
Casner[182]	56 (retrospective case series)	School-aged children in Texas – NTX: 25–300 mg/day for 3–87 mo	Therapy maintenance: 57% SIB: −74% in 25% of objective responders SAE: none
Campbell[184]	41 (PCT)	2.9- to 7.8-yr–old with autism – NTX: Up to 1 mg/kg/day for 3 wk	Hyperactivity score: NTX: −0.22, PLB: −0.36 SAE: none
Barrett[185]	1 (PCT)	12-yr-old with autism and self-injury – NTX dose not reported	"Near zero rate of self-injury" SAE: none
Feldman[23]	24 (PCT with crossover)	3.0- to 8.3-yr–old – NTX: 1.0 mg/kg for 2 wk	Median words produced: NTX: 55 (CV 153%); PLB: 64 Mean words produced: NTX: 12; PLB: 9.5 SAE: none
Kolmen[25]	11 (PCT with crossover)	3- to 8-yr–old – NTX: 1.0 mg/kg	Parent CGI-I: NTX: 3.0 (CV 30%); PLB: 4.0 Teacher CGI-I: NTX: 3.4 (CV 24%); PLB: 4.0 SAE: none
Willemsen-Swinkels[22]	23 (PCT with crossover)	3- to 7-yr–old – NTX: 0.7–1.2 mg/kg/day for 4 wk	Parent CGI-I: 45% favored NTX vs PLB Teacher CGI-I: 65% favored NTX vs PLB 35% deemed "individual drug responders" SAE: none
Bouvard[186]	10 (PCT with crossover)	5- to 14-yr–old – 0.5 mg/kg/day for 1 mo	"Strong" response: 40% No response: 30%–40% SAE: none
Campbell[187]	18 (PCT)	3- to 8-yr–old – NTX: up to 1 mg/kg/day for 21 days	Marked/moderate improvement: NTX: 67%; PLB: 11% SAE: none
Leboyer[188]	4 (PCT with crossover)	4- to 19-yr–old – NTX: 0.5, 1.0, 2.0 mg/kg/day for 7 days	Global improvement and reduced SIB: 75% displayed at small and large doses SAE: none
Gonzalez[189]	41 (PCT)	2.9 to 7.8-yr–old – NTX: up to 1 mg/kg/day for 3 wk	Global Clinical Consensus rating: NTX: marked/moderate improvement in 70% Mean weight change, kg: NTX: −0.16; PLB: −0.02 SAE: none
Kolmen[24]	13 (PCT with crossover)	3- to 8-yr–old – NTX – 1 mg/kg/day × 2 wk	Parent CGI-I: NTX: 3.0 (CV 37%); PLB: 4.3 Teacher CGI-I: NTX: 3.4 (CV 26%), PLB: 4.1 SAE: none
Scifo[190]	12 (PCT with crossover)	7- to 15-yr–old – NTX: 0.5, 1.0, 1.5 mg/kg every 48 hr for 15 wk	Symptoms (based on BSE): −27% (CV 52%) SAE: none

BSE, Behavioral Summarized Evaluation; CGI-I, Clinical Global Impressions-Improvement; CV, coefficient of variation; PCT, placebo-controlled trial; PLB, placebo; SAE, serious adverse event

are not well described. Looking again at the structurally similar compound, morphine, it appears that increasing total body weight (in morbidly obese adults) appears to only minimally impact formation of UGT2B7-dependent conjugates. It is unclear if this is clinically meaningful or will prove to be mirrored with NTX.[52]

Adults with severe liver disease, specifically those who were Child-Pugh Classes B and C, had 5- and 10-fold higher systemic exposure (i.e., area under the curve), respectively, than healthy adults.[1] Interestingly, systemic exposure to 6βN did not differ among these groups. This suggests the need for caution and potential dose adjustment if NTX is required in the setting of chronic liver disease or cirrhosis.

Excretion. Most of NTX and metabolites is renally cleared (>95%).[11] Naltrexone (free and conjugated) represents 5% to 20% of the total analyte recovered in the urine, with 6βN comprising the majority (~35%–60%). The parent is primarily excreted in its conjugated form (~95%), whereas 6βN is primarily excreted unconjugated

Table 10. Summary of Naltrexone (NTX) Efficacy and Safety in Pediatric Trials in Eating Disorders

Reference	Sample Size (Study Design)	Dosing and Duration	Outcome
Chatoor[93]	1 (case study, PCT)	15-yr–old with BN – NTX: Up to 100 mg/day for 8 days	Urge scores: NTX: 1.5 (CV 33%); PLB: 4.5 SAE: none
Stancil[15]	33 (retrospective case series)	Adolescents with AN-BP and BN –NTX: up to 100 mg/day, mean duration 129 days	Reduced urges and behaviors: 67% of participants CGI-I score: mean: 2.7 (CV 48%) SAE: none
Raingeard[12]	10 (open-label)	Mean age, 22 yr; range, 17–29 yr with type 1 diabetes and BN/binge eating – NTX: 200 mg twice daily up to 1 yr	Purge behaviors: reduced 75% (range, 52%–100%) Weekly binge-eating events: reduced 86% (range, 29%–94%) SAE: none

AN-BP, anorexia nervosa binge-purge subtype; BN, bulimia nervosa; CGI-I, Clinical Global Impressions-Improvement; CV, coefficient of variation; PCT, placebo-controlled trial; PLB, placebo; SAE, serious adverse event

(~65%).[87] The minor metabolite, 2-hydroxy-3-methoxy 6-β-naltrexol, accounts for ~10% of the total drug excreted in the urine.[35,59] Renal clearance of unconjugated NTX appears to occur primarily through glomerular filtration.[87] Tubular secretion is involved in excretion of the metabolites 6βN, NTX-conjugate, and 6βN-conjugate. Glomerular filtration rate, a marker of renal clearance, is reduced in neonates and infants, but it approaches adult values by 1 to 2 years of age.[88] If used in very young children (ages <2 years), as has been reported in a patient with Prader-Willi syndrome, the impact of reduced renal function on NTX elimination should be considered when selecting dose and dosing interval. Naltrexone has not been well studied in patients with renal impairment; thus, caution is advised in older children and adolescents with known renal disease. One small study in adults with end-stage renal disease requiring hemodialysis described ~5-fold increase in maximal exposure compared with historical healthy controls.[89] The effect of concomitant drugs that alter tubular secretion (e.g., probenecid, methotrexate, indomethacin, chlorothiazide) on total NTX excretion is not known.[90]

Renal transporters are not known to play a significant role in NTX excretion. Investigations to date have evaluated organic cation transporter (OCTs) 1 to 3, OCTN1-2, and found that NTX is not a substrate. Naltrexone is also not a substrate for the efflux transporters breast cancer resistance protein MDR2.[9,37,39] Less than 5% of the dose is recovered in stool at 24 hours after acute or chronic use.[35] It is unclear whether laxative use associated with purge behavior in adolescents with eating disorders would impact excretion of NTX, although it is not likely given the minimal fraction recovered in fecal matter.

NTX Pharmacodynamics

Mechanism of Action. Although the variable response rates observed in children may be due to developmental or genetic factors influencing disposition and systemic exposure, it is also important to consider developmental alterations or genetic variation at the site of action, which may contribute to variable response.[91,92] Naltrexone exerts its primary mechanism of action by blocking opioid receptors non-selectively. There are 3 main types of opioid receptors: μ (MOR), κ (KOR), and δ (DOR), each with a distinct set of downstream effects (Table 1) located throughout the brain and nervous system, particularly concentrated in the mesocorticolimbic pathway (Figure 2).

Naltrexone is most potent at the MOR (Table 1). Duration of MOR antagonism is dose dependent.[1,93,94] A linear correlation of NTX and 6βN systemic exposure and MOR occupancy has not been observed in humans.[45] Long residence times for NTX or 6βN at the MOR may contribute to the lack of correlation between plasma concentrations and receptor occupancy. The plasma exposure-response relationship for NTX remains unclear in adults and is unknown in children. The active metabolite 6βN may be a more potent antagonist peripherally (e.g., affecting gastrointestinal motility) than centrally (e.g., affecting analgesia and pupil constriction),[95,96] suggesting the ability to rescue opioid-induced delay in gut transit time without significant interference with analgesia. Insight of MOR ontogeny is limited to murine models, which show MOR expression at birth with a gradual increase in receptor expression and binding capacity through adulthood.[97-99] The clinical implications of MOR ontogeny on NTX response remain unclear and require prospective evaluation.

The impact of genetic variation in *OPRM1*, encoding the MOR, in predicting response to NTX is limited to alcohol use disorders. A single-nucleotide polymorphism, rs1799971 (sometimes referred to as *OPRM1* A118G), decreases MOR expression[100] and alters the binding capacity of β-endorphins.[101] Clinically, rs1799971 was associated with the decreased daily consumption of alcohol in those administered NTX, but it did not affect long-term metrics of sobriety and relapse.[102] Conversely, another evaluation in more than 600 adults with alcohol use disorder found that only carriers of rs1799971 prescribed NTX were more likely to have a good clinical

Table 11. Summary of Naltrexone (NTX) Efficacy and Safety in Pediatric Trials in Prader-Willi syndrome, Crohns Disease, and Complex Regional Pain Syndrome

Reference	Sample Size (Study Design)	Disease – Dosing and Duration	Outcome
Banga[191]	1 (case report)	Prader-Willi syndrome in a 15-yr-old male – NTX: 50 mg/day for 15 mo	Cessation of skin-picking. Resumption of behavior when NTX stopped and ceased again when NTX was restarted. SAE: none
Benjamin[192]	1 (case report)	Prader-Willi syndrome in a 9-yr-old male – NTX: up to 50 mg/day	Reduced food-seeking behavior and skin-picking. Resumption of behaviors occurred when NTX stopped and reduced again when restarted. SAE: none
Puri[193]	1 (case report)	Prader-Willi syndrome in a 13-yr-old female – NTX/bupropion: 32 mg/360 mg per day for 6 wk	Weight: 4% loss Aggression and eating habits: reduced BMI: baseline: 33.9; NTX: 32.7 SAE: none
Zlotkin[194]	4 (PCT)	Prader-Willi syndrome in a 13- to 17-yr–old obese – NTX: 50 mg twice daily for 7 days	Weight: 1.05-kg gain (CV = 65%) No change in attentiveness, alertness, mood, or nutrient intake. SAE: none
Smith[195]	14 (R, PCT)	Crohns Disease in 8- to 17-yr–old with– NTX: 0.1 mg/kg (max 4.5 mg/day) for 8 wk	PCDAI: baseline: 34.2; NTX: 21.7 (CV = 15) Remission: 25% achieved; improved: 67% SAE: none
Chopra[196]	1 (case report)	Complex regional pain syndrome in a 12-yr-old – NTX: up to 4.5 mg/day for 18 mo	Pain scores: baseline: 7–10/10 (baseline); NTX: 3–5/10 SAE: none

BMI, body mass index; CV, coefficient of variation; PCDAI, Pediatric Crohn's Disease Activity Index;; PCT, placebo-controlled trial; PLB, placebo; R, randomized; SAE, serious adverse event

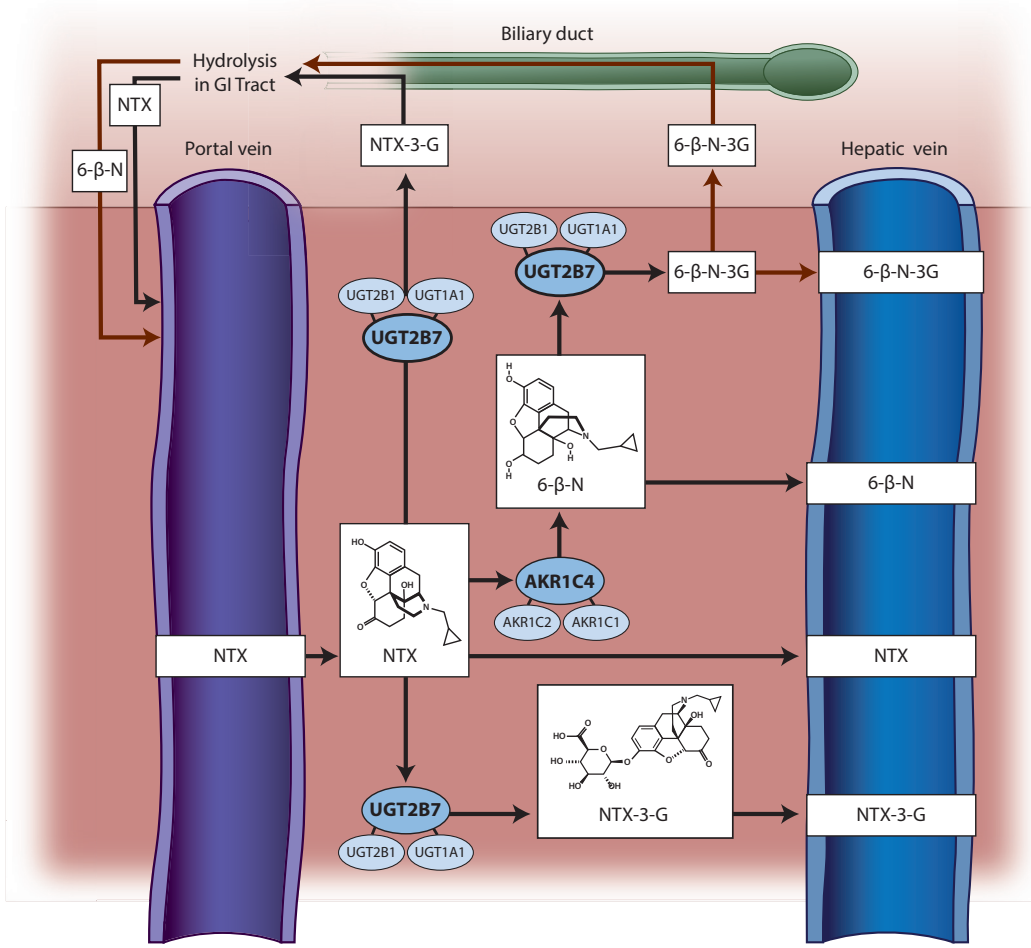
outcome that exceeded placebo response.[103] Currently, there are no data to ascertain the prognostic or predictive performance of opioid receptor single-nucleotide polymorphisms in NTX efficacy beyond addiction, including the aforementioned pediatric indications.

Although less studied, alterations in other opioid receptors may play a role in NTX's response. Naltrexone is less potent at the KOR and DOR compared with MOR (Table 1). Ontogenic patters in murine models demonstrate the presence of KOR at birth, whereas the DOR is detectable 2 weeks postnatal.[97] Similarly to the ontogenic pattern in MOR, there is a gradual increase in receptor binding for DOR in rats from infancy to adolescence, followed by a plateau extending to adulthood. The κ opioid receptor has an even more gradual incline, with a peak in adolescence and then a tailing off to adulthood.[97,98] The impact of genetic variation in *OPRK1* and *OPRD1*, the genes encoding for KOR and DOR, respectively, on NTX response is limited. *OPRK1* (rs963549; rs997917) and *OPRD1* (rs678849; rs4654327) alone or in combination have been associated with various outcomes in NTX-treated alcohol use disorder, such as days to relapse and alcohol craving[104,105]; however, further studies are needed to characterize the role of *OPRK1* and *OPRD1* in modulating NTX response.

Exposure Targets and Biomarkers. Having established pharmacokinetic exposure targets can inform the dosing strategy and reduce interindividual variability. To date, data regarding exposure targets for NTX rest solely in the adult addiction literature. Naltrexone plasma concentrations of ≥2 ng/mL provide sufficient opioid blockade to heroin challenge.[11] 6βN plasma concentrations of >40 ng/mL prevent relapse in adult alcoholics.[63] Certainly, more studies are needed to characterize the relationship between NTX exposure and clinical response including and beyond the addiction space. This may prove particularly challenging given that the action at the opioid receptor appears to exceed duration detectable in the plasma.

Pharmacodynamic biomarkers that shed light on the probability of response hold promise to aid clinicians in choosing the right drug for the right patient, particularly when response is variable among individuals with the same indication. Given NTX's mechanism of action, it is reasonable to speculate that levels of endogenous endorphins (e.g., β-endorphin, enkephalin) may vary at baseline and could provide insight into treatment sensitivity or response. As expected, NTX alters β-endorphin in plasma and cerebral spinal fluid,[93,106,107] and limited data suggest an association between NTX response and β-endorphin levels.[108-110] Opioid receptors also play a role in stress response, particularly cortisol release.

Figure 1. The naltrexone (NTX) disposition pathway in the liver.



6-β-N, 6-β-naltrexol; 6-β-N-3G, 6-β-naltrexol-3-glucuronide; AKR, aldo-ketoreductase; NTX-3-G, NTX-3-glucuronide; UGT, uridine 5′-diphospho-glucuronosyltransferase.

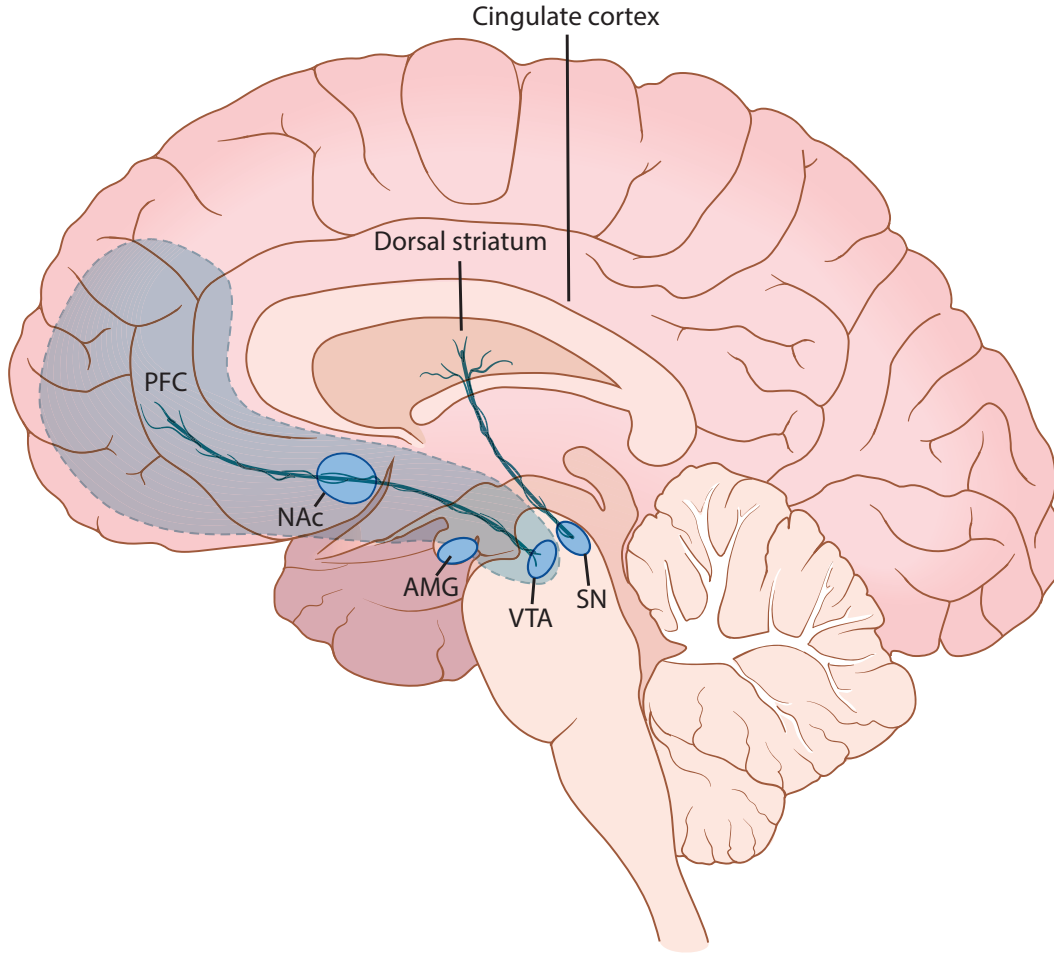
Naltrexone alters cortisol levels, an effect potentially modulated by *OPRM1* A118G genotype and sex.[111] At this time, no established or widely accepted biomarkers of NTX response exist. Future research is needed to characterize the utility of biomarkers in identifying patients that may benefit from NTX.

Practical Issues for Off-Label NTX Use in Children and Adolescents

Although a legitimate need for NTX exists in the pediatric population, access to the drug remains mired in complexity.[112-114] Payors have implemented various measures to ensure judicious use of drugs labeled for alcohol and opioid use disorders. These criteria have been reframed and refined in response to the Mental Health Parity and Addiction Equity Act legislation, Affordable Care Act coverage mandates, and the more recent opioid epidemic.[115-117] Between 2010 and 2018, NTX prescribing has increased 8.5-fold, from 64,000 to 549,000 prescriptions, and XR-NTX prescribing nearly 30-fold, from 7474 to 216,561 prescriptions.[118,119] Notably, the indications for substance use disorder also shape the criteria under which these drugs can be accessed. Across the Medicaid system, NTX and XR-NTX carry preferred status in 44 and 34 US states and territories, respectively; prior authorization requirements are required in 8 and 19 US states and territories for NTX and XR-NTX, respectively; and at least 5 and 16 US states and territories impose quantity or dosing limitations for NTX and XR-NTX, respectively, although data for this latter statistic were missing for at least one third of states.[117] These dosing limits are of particular relevance for the treatment of eating disorders where the doses that are demonstrated to be effective are more than double those approved for treating alcohol and drug dependence.

Access to NTX and XR-NTX through private insur-

Figure 2. Reward circuitry. Opioid receptors are richly distributed within the reward circuit that includes the mesocorticolimbic pathway (depicted in gray area) and nigrostriatal pathway.



AMG, amygdala; NAc, nucleus accumbens; PFC, prefrontal cortex; SN, substantia nigra; VTA, ventral tegmental area.

ance is more heterogenous.[120] Although spending for inpatient substance abuse treatment has dropped substantially among private payors, there has not been a commensurate increase in outpatient spending, and the uptake of medication-assisted treatment, under which NTX and XR-NTX fall, has been slow.[121,122] In fact, studies published from 2010 to 2015 report that only 17.3% of national substance use disorder treatment centers offered NTX, 9.1% offered XR-NTX, and their corresponding use rates are substantially lower.[123,124] Accordingly, pediatric providers are likely to incur challenges when attempting to access these medications for their patients. Definitive pediatric dosing guidance for NTX is lacking. However, Table 3 summarizes the dosing regimens previously used in various pediatric populations. Given the limited number of controlled trials, there remains a knowledge gap on optimal dosing within the pediatric population.

Pediatric-friendly NTX formulations are currently nonexistent, with only 50-mg tablets readily available. For individuals who require lower or more flexible dosing or for those who are unable to swallow pills, there are some reports of successful compounding of NTX into a liquid formulation. Naltrexone powder or commercial tablets have been compounded with preservatives (e.g., ascorbic acid, sodium benzoate) or a commercially available taste-masking suspension agent (SyrSpend SF PH4 liquid, Fagron US, St Paul, MN), with stability up to 90 days if stored at 4°C in the dark.[125,126] There is one report of crushing commercially available tablets with orange juice to yield a 1 mg/mL solution; however, stability data for this particular formulation are not available.[127] Without taste-masking, compounded NTX is described as bitter and gritty; thus, formulation palatability should not be forgotten, particularly for pediatric patients.

Conclusion

Naltrexone is a well-tolerated drug with a wide safety margin and mechanism of action that affords use across a wide variety of indications in adults and children. In addition to substance use disorders, NTX shows promise in treating conditions for which few therapeutic options exist, such as obesity, compulsivity, and eating disorders. To date, evidence regarding the disposition and efficacy of NTX is mainly derived from adult studies of substance use disorders, and considerable variability exists. Developmental changes, plausible disease-specific alterations, and genetic polymorphisms in NTX disposition and pharmacodynamic pathways should be taken into consideration when optimizing the use of NTX in the pediatric population.

In this review, the current state of the evidence has been detailed to inform the clinician. Gaps in knowledge have been highlighted to support opportunities for future research. Taken together, the information reviewed will facilitate evidence-based pharmacotherapy of mental health conditions with complex etiologies and multifaceted treatment.

Article Information

Affiliations. Division of Adolescent Medicine (SLS), Children's Mercy, Kansas City, MO; Division of Clinical Pharmacology, Toxicology and Therapeutic Innovation (SLS, SAR, JW), Children's Mercy, Kansas City, MO; Department of Pediatrics (SLS, SAR, JW), School of Medicine, University of Missouri-Kansas City, Kansas City, MO.

Correspondence. Stephani L. Stancil, PhD, APRN; slstancil@cmh.edu

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