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Novel pharmacotherapeutic strategies for treatment of opioid-induced neonatal abstinence syndrome

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Summary

The non-medical use of prescription drugs, in general, and opioids, in particular, is a national epidemic, resulting in enormous addiction rates, healthcare expenditures, and overdose deaths. Prescription opioids are overly prescribed, illegally trafficked, and frequently abused, all of which have created a new opioid addiction pathway, adding to the number of opioid-dependent newborns requiring treatment for neonatal abstinence syndrome (NAS), and contributing to challenges in effective care in maternal and fetal/neonatal (M-F/N) medicine. The standard of care for illicit or prescription opioid dependence during pregnancy is opioid agonist (methadone or buprenorphine) substitution therapy, which are also frequently abused. The next generation of pharmacotherapies for the treatment of illicit or prescription opioid addiction in the M-F/N interactional dyad must take into consideration the interplay between genetic, epigenetic, and environmental factors. Addiction to illicit drugs during pregnancy presents unique challenges to effectively treat the mother, and the developing fetus and infant after delivery. New pharmacotherapies should be safe to the developing fetus, effective in treating the physical and psychological consequences of addiction in the mother, and reduce the incidence and severity of NAS in the infant after birth. More pharmacotherapeutic options should be available to the physician such that a more individualized rather than a one-drug/strategy-fits-all approach can be used. A myriad of new and exciting pharmacotherapeutic strategies for the treatment of opioid dependence and addiction are on the horizon. This review focuses on such three strategies: (i) pharmacotherapeutic targeting of the serotonergic system; (ii) mixed opioid immunotherapeutics (vaccines); (iii) pharmacogenomics as a therapeutic strategy to insure personalized care. We review and discuss how these strategies may offer additional treatment modalities for the treatment of M-F/N during pregnancy and the treatment of the infant after birth.

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Conflict of interest statement

None declared.

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Keywords

Epigenetics; Immunotherapeutics; Mixed opioid vaccines; Neonatal abstinence syndrome; Pharmacogenomics; Serotonin syndrome

Introduction

The non-medical use of prescription drugs is a national epidemic,¹ resulting in burgeoning addiction, healthcare expenditures, and overdose deaths.² Data from the 2010 National Survey on Drug Use and Health (NSDUH) show that prescription and over-the-counter medications account for most of the frequently abused illicit drugs by high school seniors, and that nearly one-third of adolescents aged 12 years, who used drugs for the first time in 2009, began by using a prescription drug non-medically.¹ Women of child-bearing age are almost as likely as men to abuse prescription opioid medications.³ Most disturbingly, the NSDUH reports that illicit drug use is 16% among pregnant teens and 7% among pregnant women aged 18–25 years, and of women between 15 and 17 years of age the rate of prescription drug abuse is 23% in pregnant versus 13% in non-pregnant women.⁴ Although illicit drug use may be decreasing, this alarming increase in prescription drug use in pregnant women, in general, and adolescent women, in particular, is adding to a public healthcare crisis that significantly affects the outcomes of maternal and fetal/neonatal (M-F/N) interactional dyads.¹ Currently, the most frequently abused prescription drugs are: opioids, which provide superior pain management for cancer and chronic pain; benzodiazepines, which treat anxiety and sleep disorders; and stimulants, which treat attention deficit hyperactivity disorder and narcolepsy.⁴ Because prescription opioids are overly prescribed, illegally trafficked, and frequently abused, a new opioid addiction pathway has been created, adding to the number of opioid-dependent newborns requiring treatment for withdrawal or neonatal abstinence syndrome (NAS).^{2,3} In addition to NAS, illicit and prescription opioid use during pregnancy is associated with increased rates of low birth weight (<2500 g), prematurity, respiratory disease, sudden infant death syndrome, and neonatal mortality, all of which translate into lengthy hospital stays with associated healthcare expenses).^{2,3,5} Standard treatment strategies for opioid addiction during pregnancy and for NAS include opioid substitution (methadone or buprenorphine) during pregnancy and opioid replacement (morphine, methadone, buprenorphine) with the addition of clonidine⁶ or phenobarbital⁷ as adjunctive therapies for infants who need pharmacological treatment for NAS. A comprehensive review has been recently published focusing on these standard therapies,^{8,9} hence, these standard therapies are not further discussed in this review. Instead, we focus on novel therapeutic approaches and strategies for the treatment of addiction and how these strategies may be used during pregnancy and/or for the treatment of NAS. Although all classes of prescription drugs, in addition to opioids, are abused by pregnant women and can result in NAS in their neonates, this review focuses primarily on novel therapies for opioid addiction.

Neonatal abstinence syndrome

Neonatal abstinence syndrome (NAS), the behavioral manifestation of physical dependence, is characterized by a variety of somatic and autonomic signs/symptoms including high-pitched cry, hyperirritability, hypertonia, feeding intolerance, emesis, diarrhea, tremors, respiratory distress, tachypnea, and, in severe cases, seizures; and it occurs upon abrupt cessation of maternal opioid exposure.^{2,10} Although traditionally, NAS more often refers to withdrawal from in-utero exposure to opioids, it may also be used in reference to the infant who was exposed to other psychoactive substances, such as alcohol, benzodiazepines, cocaine, nicotine and, more recently, selective serotonin reuptake inhibitors (SSRI), the most frequently prescribed antidepressants.² The mechanisms underlying the signs/symptoms associated with NAS are multifactorial, unique to each pregnancy, poorly understood, and therefore it is difficult to define the pathophysiology, explain and assess the individual variability, and provide effective treatment of NAS. In this review, we focus on new treatment strategies for infants with NAS from fetal exposure to illicit or prescription opioids. Albeit, many infants exposed to opioids may have polysubstance exposure, further complicating treatment strategies.

The standard of care for opioid dependence during pregnancy is opioid agonist (methadone or buprenorphine) substitution therapy, which usually entails substituting a licit opioid for an abused illicit or prescription opioid.¹¹ Substitution therapy with methadone or buprenorphine during pregnancy is associated with improved outcomes for the M-F/N dyad.¹² Methadone maintenance or buprenorphine substitution therapy is not without its detractors as the use of these drugs is linked to physical, mental, and psychological problems for the mother and neonate.⁵ The efficacy of substitution therapy with methadone or buprenorphine in the treatment of NAS is due to the opioid agonist properties of these drugs (i.e. high abuse liability), which also confer disadvantages and limitations to their use, necessitating the development of novel, efficacious and safe pharmacotherapeutic strategies to treat opioid dependence and NAS in the M-F/N dyad.

Targeting the serotonergic system to reduce symptoms of opioid dependence

Specific serotonin receptors and opioid dependence

In humans, opioid withdrawal is characterized by affective symptoms (e.g. anxiety and depression) as well as the somatic and autonomic signs/symptoms. Opioidergic–stress–serotonergic multifactorial mechanisms appear to underlie the negative emotional symptoms of opioid withdrawal processes.¹³ Thus, the role played by serotonin (5-hydroxytryptamine, 5-HT) in the physiological and behavioral adaptations that occur during opioid withdrawal has been of considerable interest to opioid addiction researchers. Of the aminergic neurotransmitters, 5-HT is perhaps the one most implicated in the cause or treatment of various disorders (e.g. anxiety, depression, pain, nausea, etc.). Not surprisingly, 5-HT receptors, specifically the 5-HT₃ receptor (5-HT₃R), are implicated in these opioid withdrawal adaptations.¹⁴ Moreover, the 5-HT₃R modulates the activity of the mesolimbic dopaminergic system, which is an essential circuit involved in the neurobiology of addiction

to multiple substances. 5-HT₃Rs are transmitter-gated, cation-selective channels, which mediate neuronal depolarization and neurotransmitter release in the central nervous system and periphery, and many antiemetics, anesthetics, anxiolytics, and analgesics exert their effects by blocking these receptors. The 5-HT₃R is made up of A and B subunits. Morphine has been shown to upregulate expression of the A subunit encoded by the *HTR3A* gene in the amygdala, dorsal raphe, and periaqueductal gray nuclei, all of which are known to be linked to opioid dependence adaptations.¹⁴ In a well-designed study to determine the leading candidate genes modulating physical dependence to opioids in mice, Chu et al.¹⁴, combined behavioral studies in multiple strains of inbred mice with haplotype-based computational genetic analysis of the phenotypic data to demonstrate that the *HTR3A* gene was a leading candidate gene in mediating opioid dependence adaptations in mice. Ondansetron (Zofran), a selective 5-HT₃ antagonist and widely used antiemetic drug in humans, blocked many of the naloxone-precipitated withdrawal behaviors in mice. Testing their hypothesis in humans, by using an acute morphine administration paradigm, the role of 5-HT₃Rs in mediating the objective signs of withdrawal in human volunteers was confirmed.¹⁴ In this elegant series of studies, these investigators provided the first demonstration that ondansetron, a readily available 5-HT₃R antagonist, can reduce the severity of opioid withdrawal symptoms in humans.¹⁴

Ondansetron is widely used as an antiemetic in adults and children with cancer. Although not US Food and Drug Administration (FDA)-approved for use during pregnancy, it has been used off-label to reduce nausea and vomiting, especially in women with hyperemesis. In a case study of 14 women treated with ondansetron for hyperemesis gravidarum, seven of these women were given ondansetron before 11 weeks of gestation, during the period of organogenesis. One infant in the early ondansetron treatment group had a birth defect (ventricular and atrial septal defect). This mother also had diabetes type 2 which has a known association with cardiac lesions. In three other case reports describing the use of ondansetron for the treatment of hyperemesis gravidarum, all infants were born without birth defects.¹⁵ Ondansetron crosses the placenta and can be detected in all fetal compartments.¹⁶ Preclinical and clinical studies are needed to determine whether ondansetron can be used during pregnancy as an adjunctive therapy to opioid substitution, the combination of which may prove to be more efficacious than opioid therapy alone. Not surprisingly, infants born to mothers who are compliant with opioid substitution treatment programs have better outcomes than infants who are born to mothers who continue to use illicit drugs.^{3,11,12} Whether other agents targeting other receptor systems will reduce adverse effects of opioids in the fetus remains to be determined. Lastly, clinical studies to determine the safety, efficacy, pharmacokinetics, and pharmacodynamics of ondansetron in human term infants with NAS are required. 5-HT₃R signaling appears substantially to predict opioid dependency; it would be of great interest to determine whether specific polymorphisms confer additional susceptibility to addiction.

Increasing serotonin at the synapse: the effect of selective serotonin reuptake inhibitors (SSRIs) on opioid withdrawal

In addition to upregulating *HTR3a* gene expression, acute morphine administration also enhances 5-HT concentration in the dorsal raphe nucleus (DRN), where serotonergic

neurons originate.¹³ Although electrical stimulation of the DRN attenuates morphine self-administration and withdrawal symptoms, 5-HT does not appear to be required for morphine reinforcement or withdrawal,¹³ but indirect evidence suggests that drugs that increase 5-HT levels at the synapse alter the symptoms associated with opioid addiction. SSRIs (e.g. paroxetine, fluoxetine, and sertraline), a class of antidepressants that increases the amount of 5-HT in brain synapses by blocking reuptake via serotonergic neurons, are among the most frequently prescribed drugs to treat depression and anxiety in the general population and in pregnant women.¹ In a recent study by Goeldner et al.,¹³ a direct connection between opioid withdrawal and depression-like symptoms was demonstrated in adult mice. In that study, mice were exposed to a chronic escalating morphine regimen. Morphine was then stopped and the mice were examined during the withdrawal period. Serotonergic activity in the dorsal raphe remained impaired after four weeks of abstinence and was associated with low sociability and despair-like behavior in these mice. Remarkably, chronic fluoxetine prevented these behaviors.

In another study of morphine-dependent rats prior to naloxone-precipitated opioid withdrawal, acute treatment with SSRIs decreased the severity of the opioid withdrawal syndrome.¹⁷ Future studies using rodent models should elucidate the molecular alterations mediating long-term serotonergic neuroadaptations in opioid withdrawal.

Similar to adult rodents, administration of SSRIs reduces chronic morphine withdrawal symptoms in neonatal rats.¹⁸ However, in humans, SSRI exposure for the treatment of maternal depression or anxiety during pregnancy is associated with neonatal neurobehavioral disturbances in exposed infants. The use of SSRIs during the third trimester of pregnancy is linked to a cluster of neonatal signs including incessant crying, hyperirritability, hypertonicity, hypoglycemia, tremors, tachypnea, feeding and sleep disturbances, and seizures – an SSRI withdrawal syndrome that is similar to NAS seen in opioid-exposed infants.^{10,19} Also of concern when considering SSRIs for the treatment of withdrawal is a well-known 5-HT toxicity syndrome. This is a potentially fatal disorder with excessive muscle hyperactivity, clonus, hyperpyrexia, metabolic acidosis, rhabdomyolysis, and renal failure from excessive stimulation of serotonin receptors in the brain and periphery. 5-HT toxicity syndrome can occur when there is an overdose of SSRIs or concurrent use of other classes of drugs that increase 5-HT in the synaptic cleft or directly bind to 5-HTRs. These drugs include monoamine oxidase inhibitors,¹⁹ amphetamines, cocaine, sumatriptan, buspirone, hallucinogens, dextromethorphan.²⁰ Many of these drugs are used in combination recreationally by adolescents, potentially increasing the risk of morbidity to the maternal/fetal dyad.

Controversy exists as to whether neonatal neurobehavioral disturbances observed in infants exposed to SSRIs are better explained by 5-HT toxicity syndrome (attributable to increased 5-HT concentration in the synaptic cleft) or by SSRI withdrawal (attributable to a relative hyposerotonergic state).¹⁹ However, the most frequent clinical syndrome (incessant crying, hyperirritability, hypertonia, hypoglycemia, tremors, tachypnea, feeding and sleep disturbances) seen in neonates exposed to SSRIs in utero is consistent with hyperserotonergic tone (after toxicity) rather than with evolution of hyposerotonergic tone (from withdrawal).¹⁹

SSRIs are implicated in the neuroadaptations associated with opioid addiction and may be beneficial in adults. However, these drugs that increase brain serotonergic neurotransmission are not without serious and sometimes fatal consequences and should be used with caution during pregnancy, particularly in adolescents. On the other hand, many pregnant women have mood disorders that may be exacerbated during pregnancy, and, thus, SSRIs are often essential. Certainly, the interplay between genetic, epigenetic, and environmental factors contributes to the variability in NAS presentation and to the overlapping signs/symptoms of NAS, 5-HT toxicity syndrome, or SSRI withdrawal.¹⁰ It would be of considerable interest to determine the pharmacodynamics of opioid and SSRIs on maternal compliance and well-being during pregnancy, on fetal autonomic behavior, and the incidence and severity of NAS after birth. In the following section, mixed opioid immunotherapy is discussed.

Immunotherapeutics

The use of immunotherapies, including vaccines, monoclonal and catalytic antibodies, is a novel approach that may yield specific antidotes for drugs of abuse, helping to ameliorate the morbidity and mortality associated with illicit drug intoxications.²¹ Methadone and buprenorphine as treatment modalities for opioid addiction are efficacious; however, use of these opioid agonists results in marked addiction liability, targets only a narrow portion of opioid abusers, necessitates healthcare worker vigilance, and is legally restricted to established daily opioid users.²² Vaccines targeting illicit and prescription opioids of abuse are being developed as alternative or adjunctive therapies to treat dependence and addiction.^{22,23} As a potential treatment for opioid addiction, opioid conjugate vaccines show promise in animal models. For an excellent review of the design of opioid conjugate vaccines and preclinical studies see Anton et al.²⁴

Individual vaccines possess high specificity, targeting only a limited number of structurally similar opioids. In preclinical studies and clinical trials, these abuse-fighting vaccines trigger the immune system to produce high-affinity antibodies, which bind to and sequester targeted drugs of abuse before they are distributed to the brain, which, in turn, attenuates drug-induced behaviors.²³ Several opioid vaccines exist that elicit antibodies that bind heroin and its metabolites [6-monoacetylmorphine (6-MAM), morphine, and morphine-6-glucuronide] and reduce heroin- or morphine-induced self-administration in animals.^{24–26} The use of structurally specific vaccines is advantageous in that they show negligible affinity for methadone, buprenorphine, or naltrexone (a mu-opioid receptor antagonist), allowing the simultaneous use of opioid agonist therapies.

Since an increasing proportion of opioid abuse is now due to prescription opioids, there are also animal studies evaluating vaccines for these drugs. Pravetoni et al.²² recently reported the design of an oxycodone vaccine, which binds oxycodone and its active metabolite, oxymorphone. The vaccine reduced oxycodone distribution to the brain and reduced oxycodone-induced hot plate analgesia in rats. The availability of the heroin vaccine and the oxycodone vaccine presented the possibility of using a bivalent immunization strategy (i.e. combining two vaccines that target several of the most frequently abused opioids: heroin, oxycodone and their active metabolites), thereby achieving broader opioid binding activity. In another series of experiments, Pravetoni et al.²⁷ co-administered an oxycodone vaccine,

targeting oxycodone and its active metabolite oxymorphone, and a morphine vaccine, targeting heroin, 6-MAM and morphine. This strategy did not compromise the immunogenicity or efficacy of either vaccine.²⁷ As a cautionary comment, the authors state that in humans it is often more difficult for opioid vaccines to elicit very high serum antibody titers than in experimental animals. However, Anton et al.²⁴ designed a highly immunogenic morphine/heroin vaccine using tetanus toxoid as a protein carrier, which is routinely used to construct vaccines for humans.

Whereas the potential role of these vaccines in opioid dependence, preventing NAS, and addiction treatment remains unclear because these vaccines are still in the infancy stage of development, the possibility that these immunotherapeutic approaches could be used to reduce relapse during pregnancy is especially exciting. The greatest barrier to sustained abstinence from illicit drugs is the risk of relapse because of persistent drug craving that remains after many years of abstinence with relapse often being triggered by stress and drug-associated cues.²⁸ Furthermore, after a period of abstinence, a greater 'high' is achieved with illicit opioid exposure after just one 'hit', contributing to recidivism. Efficacy of antimorphine vaccines providing immunoprotection against relapse has been demonstrated in adult rodents previously taught to self-administer heroin or morphine;^{24,26} whether this immunoprotection could occur in humans is not beyond the realm of possibilities.

The optimum strategy would be for a drug-dependent woman to develop immunity prior to pregnancy with periodic booster injections to maintain high antibody titers against the targeted opioid during pregnancy. Thus, if re-exposure to illicit opioids does occur, the antibody will sequester the opioid creating an antibody-antigen complex, making it unable to cross the blood-brain barrier (preventing the 'high') or to be transferred across the placenta. Whether the anti-opioid antibodies will cross the placenta and provide some additional protection to the fetus depends on multiple factors: gestational age, and class and subclass of antibody produced). IgG is the predominate immunoglobulin that crosses the placenta via a receptor-mediated active transport. The transport system is most efficient for the IgG1 subtype followed by IgG3 and IgG4 with minimal transfer of IgG2. IgG levels in the fetus progressively increase from the second trimester to term such that total IgG concentrations can exceed maternal levels by term, by contrast with only 5–10% of maternal concentrations in the second trimester (for review see DeSesso et al.²⁸). Whereas antigen-antibody complexes do not cross the placenta, non-complexed IgG antibodies do, and the higher the titer of IgG in the mother the greater the titer of antibodies in the fetus and newborn.

In summary, opioid vaccines will probably not replace existing agonist substitution therapy but they could serve as useful adjuncts. An opioid vaccine could be useful for opioid abusers who refuse substitution therapy or who do not legally qualify for therapy because they are occasional users. Opioid vaccines may also be used as adjuncts to agonist therapy to provide efficacy during periods of agonist medication non-compliance or for those who persistently abuse opioids even while on agonist therapy. Morphine and oxycodone vaccines were designed to target illicit or prescription (heroin, morphine, oxycodone, and oxymorphone) but not therapeutic opioids (methadone, buprenorphine or naltrexone). A vaccine that blocks

a wide range of opioids of abuse may have distinct advantages in battling the widespread availability (i.e. tide) of illicit and prescription opioids of abuse.²⁷ Perhaps, in an ideal world of prevention, high-risk adolescents could be vaccinated against illicit drugs of abuse such that addiction could not occur. The biggest challenge will be to design immunotherapies such that they are efficacious for addictive behaviors but do not prevent the effectiveness of analgesics given systemically when needed for the treatment of acute and chronic pain.²⁹ Future studies should (i) determine the efficacy of anti-opioid vaccines in models of addiction during pregnancy; (ii) enhance the immunogenicity and specificity of the antigen-protein construct that can be used in humans; (iii) determine optimal 'vaccination paradigms', which will establish the pharmacodynamics of addictive behaviors and the pharmacokinetics in adolescents, adults (controlling for sex and gender), and models of addiction during pregnancy; (iv) determine whether vaccination prevents establishment of opioid addiction; (v) determine the adverse effects of these therapies as they relate to the treatment of pain in both the mother and infant.

Maternal and fetal/neonatal pharmacogenomics

Prescribing decisions will be increasingly guided by genetic tests that can predict risks and effectiveness of treatments for individual patients.³⁰ Maternal and fetal/neonatal (M-F/N) medicine is trending away from the one-drug/strategy-fits-all approach toward a more 'personalized therapy' approach. Pharmacogenomics is the field of study encompassing the genetic basis underlying individual drug response variability. The exploration of M-F/N pharmacogenomics as a new NAS treatment strategy, although in its infancy, shows promise.³¹ Briefly, pharmacogenomics examines multiple non-dominating genes suspected of affecting individual pharmacodynamic (drug action) and pharmacokinetic (body's response) parameters, and seeks to correlate a specific drug response with specific genetic variations (i.e. single-nucleotide polymorphisms, SNPs), usually in the form of gene copy number variations, deletions, or duplications, which can result in altered protein structure and function, resulting in distinctive pharmacokinetic/pharmacodynamic profiles in individuals.³¹

SNPs in the mu-opioid receptor are especially pertinent to the topic of opioid addiction and withdrawal, as this receptor is the main site of action for morphine, heroin and methadone.³² The most frequent SNP identified results from an amino acid substitution (118A→G) in the binding site of the receptor. Although this polymorphism does not alter affinity of the receptor to exogenous opioids, it does increase the affinity of the receptor to endogenous beta-endorphins by three-fold,³³ and increases the risk of addiction and alters the response to treatment. Individuals with the 118G as opposed to the 118A allele show increased response to the opiate antagonist naloxone,³⁴ and return to heavy drinking more quickly after naloxone-precipitated withdrawal.³⁵ Also of importance, the frequency of the genetic alleles is not the same across all ethnicities.³⁶ In studies that compare control with opioid-dependent adults, polymorphisms in the mu-opioid receptor confer a significant attributable risk for addiction to heroin.³⁷ Given this prior research, it seems plausible that future attempts to customize pharmacotherapy for M-F/N dyads must include consideration of allelic variants of the mu-opioid receptor.

In 2004, the FDA approved a cytochrome P(CYP)450 genotyping platform for detecting mutations that affect metabolism of opioids and other medications.³¹ The *CYP2D6* gene encodes the CYP2D6 enzyme, which is a member of the cytochrome P450 superfamily of mono-oxygenases. The CYP2D6 enzyme is polymorphically distributed and metabolizes ~25% of all medications in the human liver. It converts codeine to morphine via O-demethylation, and represents ~10% of codeine clearance. Morphine is further metabolized into morphine-6-glucuronide, which has opioid activity, and into morphine-3-glucuronide, both of which are eliminated via the kidney. Tramadol is also metabolized by the CYP2D6 enzyme. Allegaert has done some elegant work on the differential maturation of the renal elimination and genetic polymorphisms affecting tramadol metabolism during infancy.³⁸ Individuals with altered activity of the CYP2D6 enzyme variant, due to deletions and frame shift or splice-site mutations of the gene, are categorized as having poor, rapid or ultra-rapid metabolizer phenotype.³¹ For example: the CYP2D6 enzyme variant (i.e. the ultra-rapid metabolizer phenotype) converts codeine into morphine more rapidly than the normal version of this enzyme.³¹ Nursing mothers with this variant who are taking codeine secrete high levels of morphine in their breast milk, which increases the risk of overdose in their infants.³⁰ This variation has staggering implications for the treatment of opioid dependence, NAS, and addiction.

Several groups are attempting to link central pain and addiction processing pathways to genetic polymorphisms. Curatolo's group working at the clinical Trials Unit in Bern is analyzing a spectrum of these genes including oxidation reactions in the cytochrome P-450 enzymes (CYP2D6, CYP2C19, CYP3A4), haplotyping the dopaminergic gene *COMT* (a candidate for susceptibility to addiction), and the A118G mu-opioid receptor gene variants.³⁹ At Columbia University, Smiley is leading a group looking specifically at mu-opioid receptor genetics (*OPRM1*) in pain management.⁴⁰ The Children's Research Institute in Washington DC is examining the clearance of methadone and the enzymatic activity of CYP2B6 variants.⁴¹ This study led by van den Anker will determine the clearance related to gestational and postnatal age. The acquired knowledge based on these and other upcoming studies will undoubtedly lead to more efficacious and individualized treatments of opiate withdrawal syndrome in newborn infants.

Whereas genes can be modified via direct alteration of the nucleotides within the DNA, thereby altering the expression of genes that lead to modifications in translation of essential proteins (receptors, enzymes, and peptides), gene expression can also be modified by epigenetic processes. Epigenetics describe reversible changes in gene activity without alteration in its DNA, which may be inheritable if the modified DNA becomes part of the progeny. Alternatively, the changes may be stable and induce long-term changes in the cell that may not necessarily be inherited. The ultimate outcome of epigenetics is the modification of DNA and the associated proteins; modifications that determine whether or not genes are available for transcription. The main epigenetic processes and those most often studied are DNA methylation and histone modifications. DNA methylation most frequently occurs on the cytosine pyrimidine ring with the level of DNA methylation in promoter regions for specific genes being inversely related to the level of gene expression. Histones are the basic proteins that bind DNA; DNA wraps around a cluster of histone proteins

forming the nucleosome that is connected by strands of DNA. Histone proteins are either acetylated or deacetylated at the lysine residue. Histone acetylation enhances gene transcription; higher levels of histone deacetylation of the promoter site represses gene transcription; see Wong et al.⁴² and McQuown et al.⁴³ for a more thorough review of epigenetic processes. As outlined in these reviews, epigenetic processes are operative in long-term neuroplastic changes underpinning addictive behaviors associated with drug addiction. Apropos to opioid addiction, increased DNA methylation in the promoter region of the gene encoding the mu-opioid receptor is found in methadone-maintained former heroin addicts as compared with controls.⁴⁴ Neilsen et al.⁴⁴ also determined that the degree of DNA methylation is further modified by ethnicity. African-Americans have a significantly lower level of DNA methylation, and in Hispanics the degree of methylation is increased.⁴⁵ While this is an epigenetic-induced process that results from drug exposure, what is of greater interest to us is: does epigenetics contribute to vulnerability to addiction? Early-life stress is positively correlated with risk of drug addiction later in life. Schwarz et al.⁴⁶ recently reported that positive early-life experience (increased neonatal handling in rodents) decreased reinstatement of morphine condition place preference (CPP). CPP is an experimental animal model of addictive behaviors, where morphine injection is paired with one of two distinctly different environments (difference in color or floor texture). Since the environment is associated with a pleasurable experience, the morphine-exposed animal will seek that environment more frequently, while saline-treated animals will demonstrate no particular preference for either of the two environments. After a period of extinction, when the morphine-exposed animal no longer has a preferred environment, re-administration of the opioid will reinstate the animals' preference (for the initial morphine-paired). Reinstatement of the environmental preference is a model of relapse. Thus, the study by Schwarz et al.⁴⁶ suggests that positive early-life experience decreases the predisposition for relapse. These authors identified an epigenetic cause for this observation: increased neonatal handling increased microglial-specific epigenetic programming of the anti-inflammatory cytokine, interleukin (IL)-10. Opioids activate microglia in the brain and are associated with a pro-inflammatory response-inducing neuroplasticity in central brain regions associated with drug-addictive behaviors, drug craving and relapse. Positive neonatal experience upregulates the expression of IL-10, which is associated with decreased frequency of relapse in adulthood. Epigenetics is a fundamental mechanism by which genes are turned on and off at different times during development. It would be of considerable interest to determine the effects of in-utero drug exposure on epigenetic modifications of particular classes of genes involved in stress responses, learning and memory, executive function, and impulse control.

In summary, pharmacogenomics has great potential for improving treatment outcome as gene variants, affecting pharmacodynamic and pharmacokinetic factors, are identified. These genetic alterations (mutations, SNPs, epigenetic modifications) will, eventually, inform pharmacotherapeutic agent choice for optimal treatment of illicit and prescription opioid abuse.³⁰ Coupling of specific SNPs to specific fetal outcomes or pharmacological and toxicological profiles in conjunction with individual gene sequencing techniques may one day provide a veritable 'genetic blueprint' for individualized, safe and efficacious M-F/N pharmacotherapies.³¹ Because epigenetic mechanisms are dynamic and reversible, agents that can modify histones and DNA methylation could potentially be a different class

of therapeutics. The recognition and potential manipulation of interindividual differences in drug response are essential steps towards personalizing pharmacotherapy for NAS.

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Practice points

Neonatal abstinence syndrome

- Commit to personalized care for every M-F/N dyad.
- Educate healthcare workers about the variability in NAS presentation, and the possibility of the signs/symptoms of NAS presenting as 5-HT syndrome or SSRI withdrawal.
- Watch for new research on opiate vaccines and pharmacogenomics and epigenetics that may one day enable practitioners to be more proactive in preventing and predicting disease; make more informed decisions about treatment options; and realize increased therapeutic outcomes, decreased drug toxicity profiles, increase patient satisfaction, and decrease healthcare costs.

Research directions

Neonatal abstinence syndrome

- Conduct prospective cohort studies on short- and long-term outcomes of existing substitution therapies in exposed neonates.
- Develop novel pharmacotherapeutic strategies to safeguard the fetus against in-utero withdrawal and improve M-F/N long-term neurodevelopmental outcomes.

Serotonin system

- Use rodent models to elucidate the molecular basis of long-term serotonergic neuroadaptations in opioid dependence/withdrawal/addiction.
- Use rodent models to elucidate the opioidergic-stress-serotonergic mechanism(s) underlying the negative emotional symptoms of opioid withdrawal and PAWS.
- Correlate serum SSRI/5-hydroxyindoleacetic acid concentrations and brain 5-HT biomarkers with changes in clinical signs/symptoms, to differentiate SSRI withdrawal from 5-HT toxicity syndrome.
- Conduct clinical trials to determine the safety, efficacy, pharmacokinetics, and pharmacodynamics of ondansetron during pregnancy and in human term infants.

Opioid immunotherapeutics

- Address the issue of low opioid-induced antibody titers in human versus animal models.
- Determine whether opioid vaccines are efficacious antidotes in high-dose or repeated-use opioid usage paradigms.
- Develop new vaccines, monoclonal and catalytic antibodies, which will yield specific antidotes for opioids of abuse.
- Develop multivalent immunization strategies that combine two or more vaccines, targeting several of the most frequently abused opioids.
- Develop mixed multivalent strategies, which combine different vaccines targeting different classes of drugs of abuse (cocaine/nicotine/heroin) in the treatment of polysubstance addiction.

Maternal and fetal/neonatal pharmacogenomics

- Identify several human genes and their SNPs affecting the pharmacodynamic/pharmacokinetic parameters of opioids of abuse.
- Determine the SNPs that affect polysubstance addiction.
- Establish a comprehensive database for all known gene and gene variants affecting opioid addiction.

- Develop sensitive genetic diagnostic tools to quickly determine the genetic predisposition of the M-F/N dyad, to determine whether individuals are slow, fast or ultra-rapid metabolizers of opioids of abuse).