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PERSPECTIVE

Expecting medication misuse: a proactive approach to drug discovery to prevent fatal overdose

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ABSTRACT

Misuse of central nervous system (CNS) depressants (alprazolam, fentanyl, etc.) is a major cause of fatal overdose, with a high prevalence of deaths involving polydrug interactions from the victim's own prescriptions. Thus, there is an urgent need to improve the safety of CNS depressants to prevent fatalities. Pharmacological pursuits aiming to prevent harm through the design of non-addictive alternatives have either failed before clinical trials or produced mediocre treatment alternatives. Therefore, we propose a new perspective for medicinal chemists: rather than aiming to prevent misuse, we must design new central nervous system (CNS) depressants under the expectation of misuse. By shifting the design focus to partial modulators rather than full agonists, we can develop novel chemical entities (NCEs) that intrinsically minimize physical harm caused by misuse without sacrificing therapeutic efficacy. In this perspective, we provide an overview of the two most widely misused classes of medications (opioid and $GABA_A$ receptor modulators) in relation to pharmacodynamic properties and clinical outcomes. We then suggest a drug discovery pathway focused on physiological parameters. It is our opinion that this approach would dramatically decrease the lethality of overdose and improve outcomes of treatments for pain, anxiety, and withdrawal from alcohol, benzodiazepines, and opioids.

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1. Introduction

Opioids and benzodiazepines (BZDs) represent two classes of central nervous system (CNS) depressants that are among the most widely prescribed and commonly misused prescription medications [1–3]. Medication misuse (MM), as stated by the National Institute on Drug Abuse (NIDA), is defined as taking a prescription drug in any manner other than prescribed; this includes but is not limited to the use of someone else's prescription, the consumption of larger doses to feel euphoria, self-medication, and uninstructed prolonged use [4]. Although MM is often mistaken to be exclusively associated with substance use disorders (SUDs), MM pervades demographics far beyond this. Approximately one-half of the US adult population is prescribed at least one prescription medication [5], 6.4% are prescribed prescription opioids [6], and 12.6% are prescribed BZD [7]. Concerningly, the proportion of those misusing prescription medications has steadily increased over the last two decades [8]. Currently, it is estimated that anywhere from 18–45% of the US adult population has intentionally misused their prescription medication [5,9,10]. However, it should be noted that data is often limited to insurance claims, provider data, and self-reporting, making it challenging to elucidate the number of nonmedical MM and accidental overuse cases involved.

Despite alarming statistics and recent efforts to educate patients and prescribers, misuse of CNS depressants continues to be a significant contributor to fatal overdose [1,11]. Although opioid-induced respiratory depression remains a leading cause of preventable accidental death, a significant portion of these deaths now involve illicit opioids combined with prescription CNS depressants or illicit stimulants [5,12]. In stark contrast to the beginning of the opioid epidemic, the current wave has morphed into a polydrug overdose crisis [13–15]. In 2022, opioids were involved in 75% of all overdose fatalities, representing 81,806 deaths. Between 60% and 70% of these (58,497) deaths involved fentanyl and more than 10% (10,964) involved BZDs [16].

Although synthetic opioid derivatives, in combination with illicit stimulants, represent the main driver behind the lethality of today's opioid epidemic, the contribution of BZDs to lethal opioid-induced respiratory depression is poorly understood. Synergistic effects from the co-use of opioids and BZDs render an individual at least four times more likely to overdose compared to those taking an opioid alone [17]. Between 1999 and 2022, BZD-positive overdose deaths increased by almost 900% [13]. It is estimated that 15–30% of all fatal opioid-related overdoses involve BZDs [18–20].

In 2016, the FDA issued a black-box warning requiring all BZD prescribing information to be updated to address serious risks of abuse, addiction, physical dependence, and withdrawal reactions. Particular attention was given to new information on the dangers of prescribing BZDs in tandem with opioids and other CNS depressants [21–23]. It should be noted that BZD and opioid co-use was already

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Article highlights

- Despite efforts to raise awareness of risks and increase warnings, misuse of central nervous system (CNS) depressants, including opioids and benzodiazepines (BDs), remains the most common cause of prescription overdose.
- Drug discovery efforts focused on the development of non-addictive alternatives for anxiety and pain treatment have largely failed to translate to clinical efficacy, leading opioids and BZDs to continue to be utilized.
- While safe and highly effective at therapeutic doses, both opioids and BZDs are widely misused and pose high risk of respiratory-depression -induced overdose if overused or co-used with other CNS depressants such as alcohol.
- We propose medicinal chemistry efforts should be employed to optimize drug parameters of opioid and $GABA_A$ receptor modulators to maintain efficacy at therapeutic doses while minimizing life-threatening risks if misused.
- By reducing maximal receptor response we can create a ceiling effect to minimize motivation for misuse and prevent fatal consequences of misuse. Preclinical models can be employed to assess for efficacy and safety in modes of misuse as compared to full modulators.

slowly decreasing by 2013, but this black box warning greatly influenced their decline after 2016. Although the continued decline of BZD overprescribing presents itself favorably for the future of public health, concerning correlations have been drawn between this decline and the recent increase in illicit designer BZD use [17,24].

Apart from limiting over prescribing, pharmacological pursuits to mitigate harms caused by medication misuse have also been largely unsuccessful. An overwhelming amount of research has been focused on minimizing the 'desirability' of medication misuse by developing 'non-addictive' agents through the guidance of animal models of addiction [25]. Although eliminating addictive potential seems like a reasonable goal, recent efforts have proven this objective too ambitious, as eliminating drug properties associated with addictive potential tends to sacrifice drug efficacy [25,26]. Thus, efficacious medications with problematic safety profiles, like BZDs, have continued to monopolize certain treatment strategies or be substituted with mediocre alternatives. As a result, clinicians and researchers face two interrelated problems: there still remains a dangerous prescribing overlap between opioids, BZDs, and other CNS depressants, but there are no treatments available to fill the overwhelming gap that eliminating certain CNS depressants would create.

The following perspective suggests a drug discovery pathway to develop a new generation of safe and effective alternatives to two of the most commonly misused and deadly classes of medications: opioids and $GABAA_A$ receptor modulators. We begin with an overview of current opioid and $GABA_A$ receptor modulators and insights gained from their preclinical and clinical use. Drawing upon these insights, we suggest amended optimization parameters to design novel and effective opioid and $GABA_A$ receptor modulators to significantly reduce lethality if misused. Ultimately, we present a new perspective for medicinal chemists in which medication misuse is accepted as inevitable.

1.1. Classifications of medication misuse and pathophysiology of lethal outcomes

We divide MM into three main categories to organize intentions of misuse: medical MM, non-medical MM, and accidental overuse. However, the diversity of intentions behind MM must be noted, as long-term MM is not likely to produce behaviors that are clearly defined by one strict category [1]. Medical MM is defined as using one's own prescription for its intended purpose but in a dose or frequency other than prescribed [4]. This can include intentional overuse to self-medicate or to overtreat active symptoms. Non-medical MM is defined as using a prescription for reasons other than what the medication was intended for or as using another person's prescription for any reason. This includes using to produce euphoria by means of overuse or by mixing with alcohol when contraindicated [27,28]. While there are variations in the definitions of non-medical MM, we include 'using for euphoria' under non-medical MM regardless of whether the prescription belongs to the individual. We also include accidental overdose as a subtype of medication misuse, defined by the unintentional consumption of high doses of prescription medication. This being most common among individuals with multiple CNS prescriptions, mental illness, or age-related cognitive decline [29]. Although distinguishable from intentional misuse, we include accidental overuse as a subtype of medication misuse for the sake of simplicity, and to further convey the diversity of causes for lethal respiratory depression.

While it is important to acknowledge the reasons behind misuse, the potential lethal outcomes are consistent across all categories and are of utmost relevance to medicinal chemists. The physiological harm caused by misuse of CNS depressants is ultimately the result of high CNS concentrations leading to overactivation of inhibitory neurotransmission [30]. This is especially dangerous when regulatory centers of the brain are inhibited. This can cause bradycardia, respiratory depression, severe sedation, and ultimately can cause critical hypoxia, coma, and death. In the case of opioids, the overactivation of μ-opioid receptors in the brainstem slows respiration and inhibits the body's response to increased CO_2 levels which would normally trigger increased ventilation [31]. In the case of BZDs, overactivation of $GABA_A$ receptors by BZDs in the brainstem and medulla hinders the regulation of respiration and heart rate. Recent animal studies confirm that the mechanism by which BZDs and opioids synergistically decrease respiratory rate is through modification of distinct respiratory parameters [32].

1.2. Opioids

1.2.1. Overview of opioid receptors

The following presents a simplified overview of opioid receptors important for CNS depressant activity. Opioid receptors are inhibitory g-protein coupled receptors located on the dendrites, cell bodies, and axon terminals of neurons in the central nervous system. There are three types of classical opioid receptors, including mu, kappa, and delta-opioid receptors [33]. The activation of these receptors by endogenous opioids causes a cascade leading to the hyperpolarization of

the cell and inhibition of neurotransmitter release from the postsynaptic neuron [33]. This action plays a key role in managing analgesia, digestion, smell, taste, and respiration. The binding of an exogenous agonist to these receptors mimics the action of endogenous opioids and thus results in therapeutic effects similar to endogenous opioids, such as pain relief [34]. Though delta and kappa opioid receptors are involved with analgesia, mu-opioid receptors are the main contributor to opioid-induced analgesia, and, as a result, their activation has been the major target in drug development [35].

1.3. Timeline of major opioid development

1.3.1. Morphine

Opioids are a class of Schedule II narcotic medication with a long history of use as analgesics, beginning with morphine, a natural opiate. Orally ingested morphine typically fails to reach circulation, and even when administered intravenously, its poor lipid solubility leads to a slow onset of analgesic effects [36]. With these disadvantages in mind, the 1990s saw a rise in synthetic and semi-synthetic opioid development to overcome challenges with morphine's solubility, effects, and administration. Thus, more lipid-soluble compounds that are inherently more potent and faster acting were synthesized. These compounds include the powerful opioids fentanyl and alfentanil [37].

1.3.2. Methadone

Methadone was synthesized in 1938 and later used in the 1960s and 1970s as the first treatment for opioid use disorder and analgesia, respectively [38]. Methadone is a MOR agonist, NMDA antagonist, and a central serotonin-norepinephrine reuptake inhibitor (SNRI) [38]. Methadone is known to have a lower abuse potential in comparison to morphine [38]. This benefit can be attributed to its slow onset and long-half-life [39]. However, it is important to note that since methadone is a full agonist, it still poses overdose risks at high doses. Furthermore, while methadone was originally hoped to be a drug that individuals were tapered off from, research suggests that in order to maintain the benefits made through methadone use for OUD, methadone use cannot be terminated [39].

1.3.3. Fentanyl

Fentanyl was first synthesized with the intention to treat pain in 1960 and was later approved in the US as an intravenous anesthetic in 1972 [37]. In contrast to other opioids such as morphine, fentanyl does not interfere with plasma histamine and thus does not pose the same risks of inducing hypotensive events [40,41]. Additionally, its high potency enables extremely low dosing, which helps minimize impact on the peripheral system, including the liver. Ultimately, Fentanyl's superior and powerful properties at therapeutic doses over other opioids result in the drug continuing to be widely prescribed in emergency settings, as it still is today [11].

The robust efficacy of fentanyl for acute pain and safety at therapeutic doses is contrasted with its extreme danger when abused. The first clinical reports of fentanyl misuse began in the 1980s, and it only got worse from there [42,43]. The prevalence of fentanyl misuse increased throughout the 1990s and into the 2000s. In 1994, the FDA listed a warning about fentanyl, urging the prescription of fentanyl patches to only be for severe pain that less potent opioids cannot manage. Throughout the mid 2000s, illicit fentanyl overdose deaths increased with a rise in adulterated heroin and cocaine. In the mid-2010s, counterfeit pills containing non-pharmaceutical fentanyl began to appear, along with a resurgence of fentanyl-adulterated heroin and cocaine [44].

1.3.4. Naloxone

The opioid overdose reversal drug Naloxone is an example of both a success and a failure to mitigate harm caused by misuse. The medication is effective when reversing overdoses caused solely by opioids and has demonstrated efficacy in prehospital emergency medical care and take-home naloxone programs as an easy-to-use medication. The widespread use and public knowledge of this drug have saved lives and continues to be an excellent drug in the context of opioid overdose. However, naloxone is only able to act as a competitive antagonist at the mu-opioid receptors and is therefore unable to reverse overdoses caused, whether in full or partially, by a drug that targets another receptor. Therefore, naloxone is significantly less effective for polysubstance overdose involving substances outside of opioids [12]. For example, BZDs are involved in up to 30% of all opioid overdoses, but since this class of drugs does not act at the mu-opioid receptors, contributions from BZDs to opioids positive overdoses cannot be reversed by naloxone. Additionally, Naloxone's short elimination half-life limits means it is cleared too quickly to accumulate and thus often can't reach high enough concentrations necessary to combat fentanyl or buprenorphine overdoses, two extremely potent opioids [43,45].

1.3.5. Buprenorphine

Treatment for OUDs was largely replaced by buprenorphine in the early 2000s. Buprenorphine is a partial mu-opioid agonist that presents with few side effects, low toxicity, and minimal overdose risk [46,47]. When used for the treatment of pain, buprenorphine outperforms morphine and exhibits an equal effect to fentanyl in terms of analgesia at low doses [47]. Patients on fentanyl experience more nausea, while patients on morphine experience more constipation than those on buprenorphine [48]. This difference in adverse events causes patients to be less likely to discontinue treatment with buprenorphine in comparison to fentanyl and morphine [47].

Buprenorphine presents a unique polypharmacological mechanism of action, exhibiting agonism at mu-opioid receptors and antagonism at kappa and delta-opioid receptors. Buprenorphine's high-affinity binding at the mu-opioid receptors results in analgesia. At doses beyond the therapeutic range, mu-opioid agonism can also result in constipation, sedation, addiction, and respiratory depression. Buprenorphine is classified as a mu-opioid receptor partial agonist, and thus exhibits an early "ceiling effect" that significantly decreases risk for respiratory depression (although this effect is still possible). It must be noted that partial agonism does not equate to partial efficacy at therapeutic doses [47–

50]. Thus, buprenorphine has shown to be just as effective for analgesia as other opioids while exhibiting a unique safety margin against respiratory depression [51].

Other benefits of buprenorphine include favorable metabolism and excretion, fewer interactions with other drugs (including other opioids), and the ability for physicians to prescribe the medication in the outpatient setting, thereby allowing for addiction treatment by primary care physicians [49].

Even with these benefits, it has important limitations to consider. For example, buprenorphine has poor oral bioavailability. Also, although the slow onset of analgesia may decrease buprenorphine's appeal for misuse, a fast-acting opioid may be initially preferred to treat acute pain [47,52]. Buprenorphine also exhibits unique challenges with toxicity. Although rare, reports of liver damage with jaundice exist in individuals taking buprenorphine [53]. Thus, patients require regular monitoring for liver toxicity. The greatest disadvantage manifests in the uncommon event of buprenorphine-induced respiratory depression [48]. Its high affinity for the mu-opioid receptors makes buprenorphine an incredibly difficult molecule to outcompete. Including naloxone, no current antidotes can reverse buprenorphine-induced respiratory depression. Buprenorphine has a binding affinity to mu opioid receptors that is ten times greater than naloxone. Naloxone's short half-life of 30–40 min half-life makes the drug incapable of surmounting this ten-fold difference in binding affinity and, therefore, is unable to displace buprenorphine from the mu receptors. Buprenorphine's 24–60 hr half-life also adds to this effect by decreasing the longevity of any displacement naloxone is capable of achieving [54].

1.3.6. Suboxone

Of important note is suboxone which combines buprenorphine and naloxone into one drug formulation and is used as an opioid withdrawal treatment for those with a history of OUD. Buprenorphine is orally bioavailable, while naloxone is not. Thus, if taken orally, only the buprenorphine is able to have an effect. However, if injected (a method of misuse), naloxone also takes effect and initially competes with buprenorphine at the mu-opioid receptors. Therefore, the fast-acting effects of buprenorphine are reduced by naloxone and limits the motivation for misuse [55,56]. This is an example of a drug formulation that was designed under the expectation of misuse and has substantial clinical success.

1.4. Gaps

Drug discovery efforts to improve the safety of analgesics have been largely unsuccessful. Non-opioid analgesics do not offer comparable efficacy to opioids and are associated with their own risks. Some examples include COX2 inhibitors, N-type Calcium Channel blockers, and subtype-specific serotonin receptor agonism. While many of these medications with alternate mechanisms of treating pain have been useful for chronic and neuropathic pain, they are not effective in treating acute pain [57,58]. At this time, there are simply no other classes of medications that are as effective for treating acute pain than mu-opioid agonists. Additionally, only mu-opioid agonists can treat opioid withdrawal. For these reasons, it is our perspective that mu-opioid agonists will continue to be used despite the consequences.

2. $GABA_A$ receptor modulators

2.1. Overview of the $GABA_A$ receptor

$GABA_A$ receptors are fast-acting, pentameric, ionotropic receptors located on the dendrites and cell bodies of neurons in both the peripheral and central nervous systems. These receptors allow for the inward movement of chloride ions which hyperpolarizes the postsynaptic neuron and therefore causes an inhibitory postsynaptic potential [59,60]. A baseline level of $GABA_A$ receptor ($GABA_AR$) activation is necessary to maintain a functioning CNS; a deficit in GABA activity can lead to seizures and death, while overactivation leads to severe sedation, respiratory depression, bradycardia, coma, and death. Being that $GABA_ARs$ result in hyperpolarization, the binding of exogenous GABA and agonists can cause this same outcome and result in sedation among other inhibitory consequences [61]. Therefore, the $GABA_AR$ is a widely targeted binding site, especially for substances with the intended therapeutic effect of anxiolytic and anticonvulsant activity.

2.2. Timeline of major $GABA_A$ receptor modulator development

2.2.1. Alcohol

Ethanol, the active psychoactive substance in alcoholic beverages, is a $GABA_AR$ positive modulator with a long history of use. Although it has no accepted medical value today, it is the most commonly used psychoactive substance, with an estimated 70% of the population regularly consuming alcoholic beverages [62,63]. Although other targets are involved, the psychoactive effect of alcohol is largely mediated through $GABA_AR$ agonism which leads to decreased inhibitions [64]. At high levels, alcohol can cause severe sedation, respiratory depression, and death [65]. As with other $GABA_AR$ positive modulators, excessive or prolonged exposure leads to downregulation of $GABA_AR$ activity and consequential withdrawal symptoms including anxiety, insomnia, seizures, delusions, and death. Alcohol withdrawal can be fatal and is typically treated with tapering of another $GABA_AR$ positive modulator [66]. Prior to their pharmaceutical development, tapering with alcohol was utilized [67].

2.2.2. Barbiturates

Diethyl-barbituric acid, also known as barbital, was the first pharmaceutical barbiturate. It was approved for use in the early 1900s after it was accidentally discovered to induce sleep in dogs [68]. Barbiturates quickly became very popular and were widely utilized recreationally and medically for the treatment of anxiety, insomnia, alcohol withdrawal, and seizure disorders. While barbiturates proved effective, they were commonly misused and often involved in overdose fatalities. The high overdose risk is related to its intrinsic $GABA_AR$ activity. Although the mechanism was unknown at the time of their discovery, at low concentrations barbiturates act as allosteric modulators at $GABA_AR$. At high

concentrations, barbiturates can activate $GABA_AR$s directly, even in the absence of GABA. For this reason, barbiturates pose a high risk of CNS depressant-induced overdose, even if used in isolation [69,70].

2.2.3. Benzodiazepines

Librium, the first BZD, was discovered serendipitously by a Hoffman-LaRoche chemist and approved for use in 1960, followed by diazepam in 1963. BZDs represented a novel class of $GABA_AR$ modulators, and due to their improved safety profiles and maintained efficacy, largely replaced barbiturates [71]. Similar to barbiturates, BZDs act as $GABA_AR$-positive allosteric modulators (PAMs) and thus provide overlapping therapeutic effects [72]. Unlike barbiturates, however, BZDs cannot activate $GABA_AR$s directly and thus have limits to their CNS depressant effects. As a result, when taken in excess, BZDs pose significantly less risk of respiratory depression than barbiturates. This improved safety profile led prescribers to overestimate their safety, and BZDs became widely prescribed [71]. It wasn't until decades later, fueled by the advent of more potent BZDs, (i.e., alprazolam), that abuse, overdose, and withdrawal risks of BZDs began to gain attention [71]. The $GABA_AR$ mediated mechanism of BZDs wasn't discovered until the 1980's, more than 15 years after their discovery. Since then, major advances in GABAergic research has led to important insights into the involvement of $GABA_AR$s in a multitude of pathological pathways, including chronic pain, depression, anxiety, epilepsy, and addiction [73].

2.2.4. Z-Drugs

Z-Drugs, also known as nonbenzodiazepines, were approved for use in the 1980s. They are a class of $GABA_AR$ PAMs that bind to the same site as BZDs but have different chemical structures [74]. Zopiclone, zolpidem, and zaleplon were the first to enter the market, and are used exclusively for insomnia. The difference in efficacy for insomnia versus anxiolysis is in the subtype selectivity of Z-drugs versus BZDs. Z-drugs are selective for alpha1 subtypes of $GABA_AR$s (subtype responsible for sedative properties), while BZDs are unselective for α1,2,3,5 subtypes, and thus provide both anxiolytic and sedative properties [75].

2.3. Drug discovery efforts

Over 40 years ago, the discovery that $GABA_AR$ subtypes have distinct functionality led to significant efforts to develop subtype selective, non-addictive $GABA_AR$ positive modulators for anxiety. This was done through the optimization of non-benzodiazepine structures, with the aim of eliminating sedative properties and reducing abuse potential while maintaining anxiolytic effects [76,77]. However, separating anxiolytic from sedative properties proved an unrealistic endpoint, and efforts to improve the safety of $GABA_AR$s have waned. However, the information obtained from their clinical use provides important insights. For instance, alpidem was an unselective partial $GABA_AR$ that was briefly approved for use in France. It was quickly withdrawn due to liver toxicity (due to structural limitations), but prior to that, demonstrated comparable efficacy and reduced overdose risks as compared to full $GABA_AR$ PAMs [74]. This demonstrates that there is substantial room for improvement in safety parameters and the feasibility of optimization to reduce risks without compromising efficacy.

2.4. Gaps

Currently, the only FDA-approved treatments for fast-acting relief of anxiety are full $GABA_AR$ PAMs. New formulations that modify pharmacokinetics (PK) properties of full $GABA_AR$ PAMs, such as Xanax XR, have not been sufficient at eliminating safety concerns, and there remains a lack of effective alternatives that can be safely prescribed to those with SUDs [78,79]. One reason this is particularly problematic is that $GABA_AR$ PAMs are necessary to treat alcohol and BZD physical dependence, yet, the only available medications are not safe in outpatient settings due to high risk of misuse in these populations [80,81]. Thus, treatment from alcohol and BZD withdrawal requires inpatient treatment with a BZD taper, a hurdle that prevents many from entering treatment. Currently, there are no treatments comparable to that of buprenorphine which can be safely prescribed to outpatients in those with alcohol or BZD physical dependence. This severely limits the likelihood of recovery and adds substantial costs [82,83].

2.5. In vivo pharmacovigilance & animal models of addiction

New CNS drugs are required to undergo a range of animal safety and abuse potential studies prior to human abuse potential studies (HABs). The required animal models include behavioral models (Irwin test, motor performance tests, self-administration study, conditioned place preference), are drug discrimination a focus on behavioral models of addiction) and physical dependence studies [84,85]. The aim of the animal studies is to screen for rewarding properties and effects similar to other drugs of abuse. The doses used for animal studies are set at 2–3 times the C_{max} since recreational use of drugs is , typically, well above the therapeutic dose [86]. However, it is important to note that animal abuse models do not need to characterize the entire dose response curve (i.e., "no effect to incapacitating levels"). As per the FDA, "This is because most animal abuse-related studies are specialized safety studies, not studies that investigate the toxicological properties of a test drug" [85,87]. As a consequence of this, toxicology studies, which include lethal doses which are more representative of overdose risks, are considered separately from abuse potential. While reports of overdose during clinical trials are considered, this is not sufficient to predict overdose risks in modes of common misuse [86,88].

2.6. Clinical outcomes in relation to drug properties

Commonly used opiate and $GABA_A$ receptor modulators with intrinsic activity, potency, approved indications, pharmacokinetic (PK) properties, are included in Tables 1 and 2, respectively [89–99].

Table 1. Commonly used opiate receptor modulators with intrinsic activity at the opioid receptor, potency, approved indications, pharmacokinetic (PK) properties, and relative estimate of overdose risks [89–92,111–113].

Medication	Indication	Receptor Activity	Relative Potency*	Oral Bioavailability	Duration of Onset	T1/2 (hours)	Metabolic Pathway	Overdose Risk**
Buprenorphine*	Opioid withdrawal, analgesia	Partial MOP agonist DOP, KOP antagonist	50	Low	Slow	3–4	CYP3A, CYP2CB UGT	Medium
Methadone	Opioid withdrawal, Analgesia	Full MOP agonist	1	High	Slow	8–59	CYP3A	Medium
Tramadol	Analgesia	Full MOP agonist SNRI	0.25	High	Med	6.7	CYP3A CYP2D6	Low
Morphine	Analgesia	MOP agonist	1	High	Med	3	CYP3A	High
Codeine	Analgesia	Full MOP agonist	0.16	Med	Med	3.5	CYP3A CYP2D6	Low
Oxycodone	Analgesia	Full MOP agonist	1	Med	Fast	3.7	CYP3A CYP2D6	High
Oliceridine	Analgesia	Full MOP agonist	3	None	Fast	1.3–3	CYP3A CYP2D6	Low
Hydromorphone	Analgesia	Full MOP agonist	8	Med	Fast	2.6	UGT2B7 UGT1A3	High
Fentanyl	Analgesia	MOP agonist	100	High	Fast	3	CYP3A	High
Naloxone	Opioid overdose	Full MOP antagonist	1000	None	Fast	1.2	UGT	None

*potency is reported relative to that of morphine.**overdose risks are estimates based on available clinical data, receptor activity, potency, duration of onset, and $T_{1/2}$. SNRI: serotonin norepinephrine reuptake inhibitor.

Table 2. Commonly used $GABA_A$ receptor modulators with intrinsic activity at the $GABA_A$ receptor, potency, approved indications, pharmacokinetic (PK) properties, and relative estimates of overdose risks [93–96].

Medication	Indication	Receptor Activity	Relative Potency	Oral Bioavailability	Duration of Onset	T1/2 (hours)	Metabolic Pathway	Overdose Risk**
Oxazepam	Anxiety, alcohol withdrawal	Full $GABA_AR$ PAM	0.25	High	Slow	5–10	UGT2B1 UGT1A9 UGT2B7	Low
Diazepam	Anxiety Alcohol withdrawal	Full $GABA_AR$ PAM	1	High	Med	100	CYP3A4 CYP2C19	Med
Lorazepam	Anxiety, alcohol withdrawal	Full $GABA_AR$ PAM	5	High	Med	12–18	UGT2B1	High
Clonazepam	Anxiety, alcohol withdrawal	Full $GABA_AR$ PAM	20	High	Med	30–40	CYP3A NAT2	High
Flumazenil	BZD overdose	BZD antagonist	10	None	Fast	0.6	CYP3A4 CYP3A5	None
Alprazolam	Anxiety, Alcohol withdrawal	Full $GABA_AR$ PAM	10	High	Fast	11–16	CYP3A4 CYP3A5	High
Triazolam	Insomnia	Full $GABA_AR$ PAM	8	High	Fast	1.5–5.5	CYP3A4 CYP3A5	Low

*potency is reported relative to that of diazepam. PAM: positive allosteric modulator. **overdose risks are estimated based on available clinical data receptor activity, potency, duration of onset, and $T_{1/2}$.

2.6.1. Potency

The binding affinity, determining compound potency, is another important parameter that has influenced the outcomes of CNS depressants. Pharmaceutical opioids and $GABA_AR$ modulators began with weakly potent compounds that were later replaced by highly potent alternatives. For instance, morphine has largely been replaced by fentanyl, and diazepam by alprazolam [37]. This increase in potency correlates with rising levels of fatal overdose. Although potency doesn't directly impact overdose potential at maximal doses, the low dosing makes it easier to accidentally consume a toxic dose [100]. Despite these risks, the high potency opioids and BZD remain widely prescribed. This is likely because of the benefits high-potency compounds provide, such as reduced off-target effects and stress on the peripheral system. This is especially important when long-term dosing is required, or treatment in those with chronic illnesses.

2.6.2. Onset and duration of action

The onset and duration of action play important roles in the addictive potential of compounds. Generally, the faster the onset, the more likely the compounds are to be misused [101]. An example of this is the difference in use of fentanyl versus the methadone. Both compounds are highly potent, full mu-opioid agonists, but methadone has a slow onset and long duration of action. This makes methadone less desirable and fentanyl more desirable for recreational use, where quick spikes in drug exposure are desired [102].

2.6.3. Intrinsic activity

The maximal intrinsic activity (IA_{max}) of a compound is the maximal receptor response that occurs at the highest doses. This is an important parameter that determines the risks of medication overuse. We hypothesize that the IA_{max} of opioid and $GABA_A$ receptor modulators is directly correlated with overdose risks, as represented theoretically in Figure 1. Full opioids, such as fentanyl, have an IA_{max} consistent with opioid receptor activation to the maximal extent. For this reason, full mu-opioids have the potential to cause respiratory depression-induced overdose, while buprenorphine, a partial opioid agonist, has significantly reduced overdose risk [103]. BZDs are

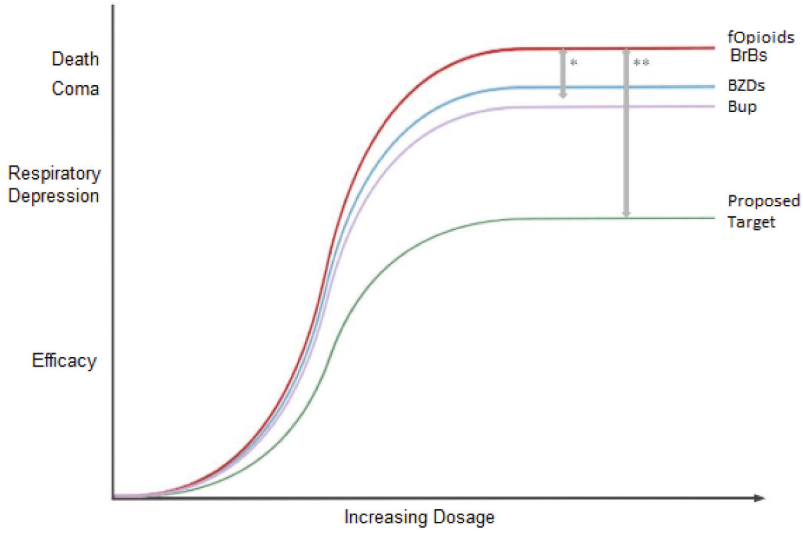

Figure 1. Theoretical representation of maximal dose response curve of opioid and $GABA_A$ receptor modulators, demonstrating the relationship between intrinsic efficacy (IA_{max}) and the overdose risks the X axis represents drug dosage, and the Y axis represents the corresponding CNS depressant effects. Abbreviations are as follows, fOpioids: full opioid agonists (red), BrBs: barbiturates (red), BZDs: benzodiazepines (blue), and Bup: buprenorphine (purple). The proposed target, or ideal IA_{max} for opioid agonists and $GABA_AR$ (green) is still unclear.

considered full allosteric modulators (distinct from agonists) because their binding leads to maximal allosteric enhancement of activity, but still requires the presence of the endogenous agonist, GABA, to be present. This is in contrast to barbiturates, which act as allosteric modulators at low concentrations and agonists at high concentrations. For this reason, barbiturates pose greater overdose risks than BZDs [69,70].

2.6.4. Positive modulation and physical dependence

Physical dependence and withdrawal symptoms are the consequence of repeated or excessive use of a substance. Physical dependence results from the neuroplastic changes that occur to compensate for over-activation of the receptor, leading to compensatory under-activation when the substance is not present, which manifests as withdrawal symptoms [104,105]. As a result, withdrawal symptoms typically include effects opposite to that of the substance. For example, symptoms of BZD withdrawal include anxiety and seizures (as opposed to anxiolysis and anticonvulsant properties associated with their use). Since withdrawal results from the under-activation of the targeted receptor, treating withdrawal symptoms requires activation of the receptor with a slow tapering in dose to allow more gradual neuroplastic adjustments [106].

2.7. Future directions

The aforementioned successes and failures to mitigate harms caused by medication misuse lead to a simple conclusion: a new perspective on drug discovery is necessary. Following the example of buprenorphine, we argue in favor of partial modulators rather than full agonists. Partial modulators are capable of reaching the same therapeutic effects as full agonists while also reducing side effects and the potential for overdose. Therefore, partial modulators are the better option when designing drugs with euphoric profiles. The development of novel opioid derivatives that are partial modulators would significantly decrease the lethality of these medications, saving numerous lives when these drugs are inevitably misused.

We argue in favor of partial modulators not only in the context of medication misuse but also for the treatment of withdrawal. Partial modulators have the potential to ease withdrawal symptoms during down-titration and could create new opportunities for outpatient BZD or alcohol detoxification. BZDs, typically diazepam, are used for individuals going through alcohol withdrawal to prevent seizures or other adverse effects. However, withdrawal from BZDs, including *diazepam*, also causes seizures that need to be prevented through a lengthy tapering. It is evident that novel chemical entities are required to increase the safety of commonly misused medications. Based on successes with buprenorphine and alpidem, partial modulators seem to be valid candidates to fill this gap. The following sections outline our suggested approach to develop promising NCE that maintain efficacy while mitigating harm.

2.8. Optimization of receptor activity

Limiting the effect of CNS depressants by reducing the maximal receptor response is a critical step toward improving the safety of opioid agonists and $GABA_AR$ PAMs. The ideal IA_{max} for opioids and $GABA_AR$ PAMs is unclear, but clinical evidence suggests that maintaining an IA_{max} between therapeutic efficacy and risk for severe sedition would prevent lethal outcomes. There are already some partial opioids and $GABA_A$ R PAMs that can be utilized to explore the relationship between in vitro IA_{max} and in vivo manifestations. However, it is important to note that the range of IAmax of current compounds is highly limited, and each has limitations preventing their development. It is for this reason medicinal chemistry efforts are required to develop new chemical entities that can overcome these limitations.

As new analogues are developed to modify the IA_{MAX}, it is likely that potency and PK parameters will also have to be improved. Since there are benefits to high binding affinities,

we suggest optimizing toward highly potent, partial modulators. Unlike with full modulators, increased potency will not increase overdose risks, as creating a ceiling effect at the receptor will eliminate the risk of severe sedation. The ideal PK parameters depend on the intended indication. For instance, if the aim is to develop a partial mu-opioid for acute analgesia, a fast onset and short duration of action would be beneficial, especially for emergency medical situations where respiratory depression risks are unknown. On the other hand, if the indication is for treatment of OUD, a slow-onset, long half-life would be desirable.

2.9. Animal studies to identify safe alternatives

Drug discovery efforts to improve the safety of opioids have largely focused on reducing abuse potential through alternate mechanisms. However, the use of behavioral models of addiction has led to poor translation from animals to humans, demonstrating a need to shift the target to a more translatable endpoint. While physical dependence and toxicology can be measured, abuse potential is a psychological phenomenon that is challenging to adequately model in animals [107,108].

2.10. Proposed drug discovery pathway

We propose a drug discovery pathway (Figure 2) that can be utilized to develop novel opioid agonists and $GABA_AR$ PAMs that maintain efficacy and minimize overdose risk. The first step includes in vitro optimization of activity, where we suggest reducing the IA_{max} to create a ceiling effect and maintaining or enhancing potency. In vivo studies may occur cyclically with in vitro studies until the ideal properties are identified. We suggest that PK properties are also optimized to minimize abuse potential (extended half-life, slow onset) but priority should be placed on activity at the receptor as PK limitations can often be overcome with new formulations, while receptor activity cannot. Animal models for efficacy should be assessed for both initial indication (i.e., opioids – analgesia, $GABA_AR$ PAMs – anxiolytic) and for efficacy in treating withdrawal from full modulators, such as opioid, alcohol, and BZDs.

There is an abundance of evidence supporting the feasibility of small-molecule optimization at $GABA_AR$ and opioid receptors. For one, it has been previously done with full opioid agonists and $GABA_AR$ PAMs. There are already easily accessible chemical structures with which we can build upon, and even crystal and cryo-EM structures we can utilize [109–111]. Additionally, the advancement of AI tools can streamline the process of optimization of chemical structure toward the desired activity. Both opioids and $GABA_AR$ are clinically validated targets with well-established animal models to screen for efficacy and physical dependence. Collectively, this makes partial opioid and $GABA_AR$ PAMs highly feasible targets and likely to translate to clinical efficacy.

3. Emerging therapies

Alterations of drug formulations with the expectation of misuse have proven an effective, although limited approach at reducing harm. The FDA has and continues to support the

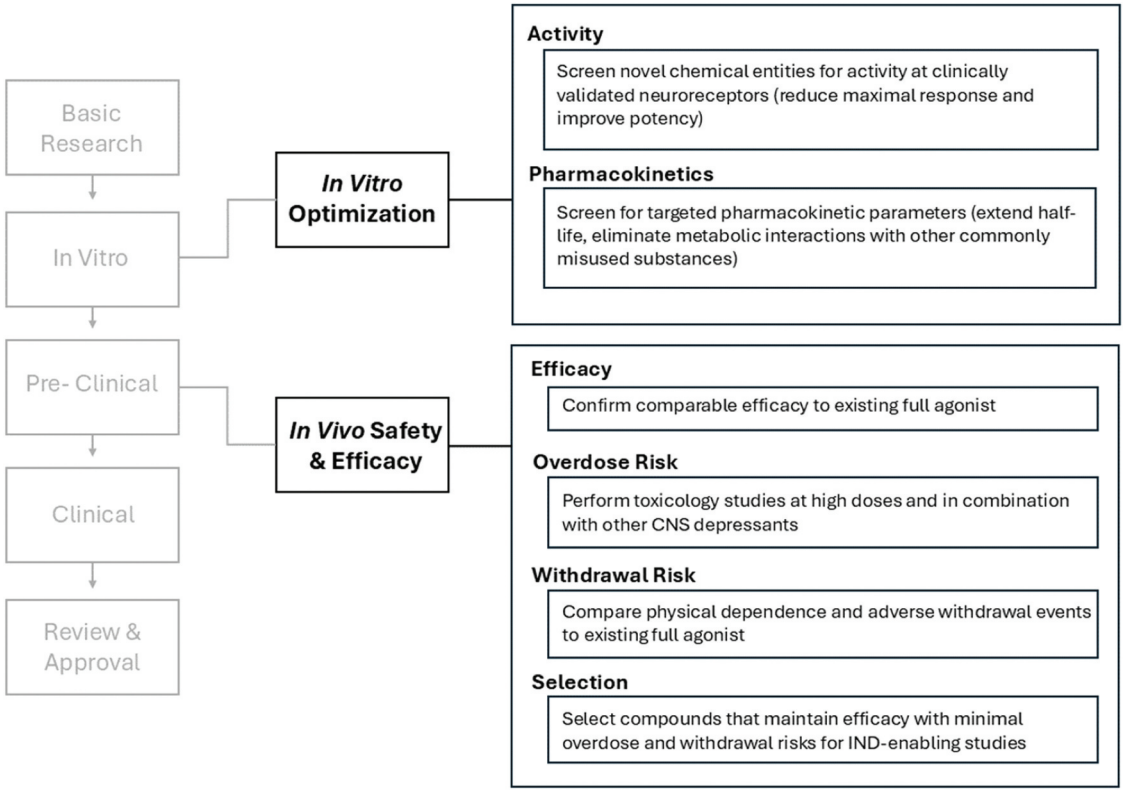

Figure 2. Proposed drug discovery pathway that can be used to optimize activity at opioid and $GABA_A$ receptors. It is important to note that a cyclic relationship between in vitro and in vivo optimization is likely necessary as in vivo data will be necessary to determine ideal optimization parameters.

development of abuse-deterrent formulations (ADFs) of commonly misused medications. However, while modifying drug formulations can alter PK properties, only structural modifications can change the intrinsic receptor activity and create a ceiling effect. It is for this reason medicinal chemistry efforts are necessary to adequately improve the safety of CNS depressant medications.

There have been a few partial mu-opioid agonists developed, including buprenorphine. Buprenorphine remains widely utilized for OUD treatment but lacks utility for acute pain relief due to its slow-onset and long half-life [46,47]. Oliceridine is a partial mu-opioid receptor agonist that was approved for use in the US in 2020. In clinical trials, Oliceridine was as effective as morphine at alleviating pain and had reduced respiratory burden suggesting improved safety over morphine [112]. However, respiratory depression risks were still present at high doses and if co-used with BZDs. The main limitation of Oliceridine is its lack of oral bioavailability and low potency, restricting its use to in-patient settings [113]. While Oliceridine provides evidence that modifying mu-opioid receptor activity can improve safety while maintaining efficacy, further medicinal chemistry is still necessary to further reduce respiratory depression risk and enhance bioavailability to enable oral dosing [114,115].

Since the failure to develop non-sedating subtype selective $GABA_AR$ PAMs, medicinal chemistry efforts to improve their safety have become almost non-existent. This gap is what inspired our research efforts at Zena Therapeutics Inc., a small-molecule Rutgers University spin-off company. We are developing of a novel class of partial $GABA_AR$ PAMs [116], with the aim of maintaining efficacy and eliminating fatal risks with misuse. Although our work is in the early stages, we have been successful in obtaining preclinical proof-of-concept data that has strengthened our conviction in the potential of reducing the IA_{max} to improve the safety of CNS depressant medications.

4. Conclusion

Opioid and $GABA_A$ receptor modulators are classes of CNS depressants that have been utilized for centuries. As more potent pharmaceuticals began to replace natural alternatives in the 1900s, both their utility and fatal consequences of misuse have increased. Despite risks, the integral role these classes of medications play in healthcare ensure their continued use. Efforts to raise awareness and prevent misuse have been unsuccessful. Thus, we propose that it is time to accept that medication misuse of CNS depressants is inevitable, and drug discovery efforts should focus on minimizing physiological harms caused by misuse. Successful drug formulations, such as suboxone, that have adopted a similar approach show it is an effective path toward reducing harms, yet there has been a lack of medicinal chemistry efforts toward this aim. Drug discovery efforts to improve safety have focused on reducing abuse potential with behavior models of addiction, and less established mechanisms of action. This has led to poor translation, with failure often due to an inability to reach adequate efficacy in the clinic. Thus, we suggest it's most realistic to improve safety by reducing the maximal receptor response. In doing so, we can maintain the benefits that come with high potency and efficacy at therapeutic doses while eliminating fatal risks associated with misuse. This perspective proposes a roadmap for future drug discovery efforts that can be utilized toward this aim, to drastically reduce fatal risk of two of the most widely utilized and dangerous classes of prescription medications.

5. Future perspective

Over the next 5–10 years, we predict there will be increased societal and political pressure to raise safety standards of pharmaceutical products, including, but not limited to, eliminating fatal consequences of their misuse. This will lead to a re-invigoration of medicinal chemistry efforts to improve safety at clinically validated targets, including $GABA_A$ and opioid receptors. Additionally, the advent of new tools such as artificial intelligence and improved methods of crystallography will facilitate more rapid and efficient optimization. This will lead to the discovery of highly potent partial $GABA_AR$ PAMs and mu-opioid receptor agonists with equal efficacy to the currently utilized full modulators without potentially fatal risks if misused. Adoption of their use will occur in almost all clinical settings, similar to how BZDs largely replaced barbiturates when their comparatively reduced overdose risks were discovered. Either preceding this or resulting from rising awareness of the feasibility of this approach, we predict the FDA will raise safety standards for acceptable therapeutic indexes of commonly misused classes of medications.

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Declaration of interest

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