HHS Public Access

Author manuscript

Peptides. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Peptides. 2019 February ; 112: 23–31. doi:10.1016/j.peptides.2018.10.007.

Determinants of Opioid Abuse Potential:Insights Using Intracranial Self-Stimulation

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Abstract

Intracranial self-stimulation (ICSS) is one procedure that can be used for preclinical abuse potential assessment. In ICSS procedures, subjects with microelectrodes implanted into a brain-reward region are trained to press an operant response lever for pulses of electrical brain stimulation, and drugs are evaluated for their effectiveness to increase or "facilitate" ICSS responding (an abuse-related effect) or to depress ICSS responding (an abuse-limiting effect). ICSS has been used for decades to evaluate determinants of opioid abuse potential, and this article reviews pharmacological and biological determinants of opioid abuse potential as revealed by ICSS studies in rodents. One of the most important observations from ICSS studies is that abused mu opioid receptor (MOR) agonists like morphine often fail to produce abuse-related ICSS facilitation in opioid-naïve subjects, but several days of repeated opioid exposure is sufficient for opioid-induced facilitation to emerge. Future studies with ICSS could help (a) to clarify mechanisms that increase MOR agonist abuse potential during early opioid exposure or during chronic exposure leading to dependence, (b) to evaluate novel opioids either developed as candidate analgesics with reduced abuse potential or identified as designer opioids being synthesized and distributed for illicit use, and (c) to test candidate pharmacotherapies for treatment of opioid abuse in non-dependent and dependent subjects.

Keywords

Intracranial self-stimulation; abuse; mu opioid receptor; mu opioid agonist

1. Introduction

Morphine and other drugs acting as agonists at mu opioid receptors (MORs) are clinically invaluable for treatment of pain and some other disorders such as diarrhea and cough. However, MOR agonists also have high abuse liability, and convergent events that include excessive prescription of opioid analgesics and increased availability of illicit heroin,

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fentanyl, and designer opioids have contributed to escalating rates of opioid abuse and overdose deaths in the United States [1]. This rise in opioid abuse has stimulated renewed efforts to develop both novel analgesics with reduced abuse liability and novel treatments for opioid abuse and overdose. Research to address these issues depends in part on preclinical assays to examine the expression, determinants, and treatment of abuse-related opioid effects. Intracranial self-stimulation (ICSS) is one family of experimental procedures that has proven useful for this purpose [2–5].

In ICSS procedures, experimental subjects (usually rats or mice) are equipped with microelectrodes targeting a brain-reward area and trained to emit an operant response (e.g. press a response lever) to receive pulses of electrical brain stimulation. During daily experimental sessions, the frequency or intensity of brain stimulation can be rapidly and precisely manipulated from low frequencies/intensities that maintain little or no responding to high frequencies/intensities that maintain high rates of responding. For example, Figure 1 shows data from male Sprague-Dawley rats with electrodes implanted in the medial forebrain bundle and trained to respond for brain stimulation under a “frequency-rate” procedure, in which increasing frequencies of brain stimulation maintain increasing rates of lever-press responding [4, 6]. Once rats are trained to emit reliable baseline frequency-rate curves, then drug effects can be evaluated for evidence of abuse-related effects. For example, Figure 1 also compares the effects of the dopamine/norepinephrine releaser amphetamine and the serotonin releaser fenfluramine, which have high and low abuse liability respectively [6]. Amphetamine dose-dependently increased (or “facilitated”) low ICSS rates maintained by low brain-stimulation frequencies and produced leftward shifts in the frequency-rate curves. This profile of ICSS facilitation is characteristic of abused drugs. Conversely, fenfluramine failed to facilitate ICSS up to a dose that decreased (or “depressed”) high ICSS rates maintained by high brain-stimulation frequencies, and this failure to produce facilitation up to doses that produce ICSS depression is characteristic of drugs that lack abuse liability. Moreover, drug effectiveness to facilitate ICSS is highly correlated with drug effectiveness to produce abuse-related effects in drug self-administration procedures, which are also commonly used for preclinical abuse potential assessment [4]. This article reviews pharmacological and biological determinants of opioid abuse potential as revealed by ICSS studies in rodents.

2. Effects of acute and repeated treatment with systemic morphine

Abused psychostimulants like amphetamine produce dose-dependent and robust ICSS facilitation in drug-naïve subjects, and these effects are retained after regimens of repeated administration [7–9]. Despite being a drug of abuse, morphine often produces a different profile of effects. For example, in opioid-naïve male Sprague-Dawley rats, morphine produces only ICSS depression during the first few hours after its administration, although ICSS facilitation may emerge at later times after initial ICSS depression has dissipated [10, 11]. Moreover, this initial profile of morphine effects often evolves during repeated treatment such that ICSS depression declines and ICSS facilitation becomes both more pronounced and occurs earlier in the time course of drug effects. For example, Figure 2 shows the effects of an ascending series of morphine doses administered at 1-hr intervals to 20 opioid-naïve male Sprague-Dawley rats [12]. No dose of morphine produced significant

ICSS facilitation at any frequency of brain stimulation, and only dose-dependent ICSS depression was observed. These rats were subsequently divided into three groups that received repeated treatment for 7 days with either saline, 1.0 mg/kg/day morphine, or 3.2 mg/kg/day morphine. At the end of this treatment period, the morphine dose-effect curve was redetermined, and Figure 2 highlights the effects of 3.2 mg/kg morphine in each group. After repeated treatment with saline or 1.0 mg/kg/day morphine, there was still little evidence of ICSS facilitation, and there remained a tendency for ICSS depression at high brain-stimulation frequencies. However, after treatment with 3.2 mg/kg/day morphine, morphine produced more robust ICSS facilitation at intermediate brain stimulation frequencies and little or no ICSS depression at higher brain-stimulation frequencies. These results are consistent with other evidence to suggest that repeated morphine administration can produce tolerance to initial ICSS depression and enhanced and accelerated expression of abuse-related ICSS facilitation [10, 11, 13, 14]. The transition from ICSS depression to ICSS facilitation after regimens of repeated morphine treatment is also consistent with clinical evidence that morphine and other MOR agonists often produce dysphoric effects in opioid-naïve humans but euphoric effects in more opioid-experienced subjects [15, 16]. Moreover, the relatively rapid emergence of morphine-induced ICSS facilitation after only a few days of morphine exposure is also consistent with evidence from the Center for Disease Control that clinically prescribed opioid exposure for as few as five days can increase risk of long-term opioid use [17].

This profile of morphine effects on ICSS is different not only from that produced by psychostimulants like amphetamine, but also by drugs from other drug classes. Specifically, we have identified three general profiles of ICSS effects that can occur during chronic treatment with drugs that produce primarily ICSS depression in drug-naïve subjects: (1) tolerance to ICSS depression and emergence of ICSS facilitation such as that described here with mu opioid receptor agonists or with high nicotine doses [18], (2) tolerance to ICSS depression without emergence of ICSS facilitation [e.g. with cannabinoid receptor agonists like Δ9-tetrahydrocannabinol [19, 20], the N-methyl-D-aspartate glutamate receptor antagonist ketamine [21], the delta opioid receptor agonist SNC80 [22], and the serotonin releaser fenfluramine [23]], or (3) sustained ICSS depression [e.g. with the kappa agonist salvinorin A [24], the dopamine D2 agonist quinpirole [22], and the serotonin 5HT1A/2A receptor agonist flibanserin [25]]. In general, drugs that produce ICSS facilitation initially and/or after repeated treatment (Profile 1) also display other signs of preclinical abuse potential (e.g. reinforcing effects in drug self-administration procedures) and have abuse liability in humans, whereas drugs that produce sustained ICSS depression do not [4]. However, drugs with the second profile of effects during repeated treatment (i.e. tolerance to initial ICSS depression without emergence of ICSS facilitation) may or may not function as effective reinforcers in drug self administration studies and/or maintain some level of abuse in humans [26–29].

Regimens of repeated morphine treatment that increase expression of ICSS facilitation by subsequent morphine doses can also produce signs of physical dependence if subsequent morphine doses are withheld (i.e. spontaneous withdrawal) or if an antagonist is administered (i.e. precipitated withdrawal) [30–34]. For example, Figure 3 shows ICSS frequency-rate curves collected before, during, or after repeated treatment with saline or

different morphine doses [31]. Before initiation of repeated treatment, electrical brain stimulation maintained a typical frequency-dependent increase in ICSS rates. When ICSS curves were redetermined 1 day after repeated treatment with saline, the ICSS frequency-rate curve was not altered. However, withdrawal for 1 day from repeated treatment with 3.2 or 18 mg/kg/day morphine produced dose-dependent rightward shifts in ICSS frequency-rate curves that occurred together with dose-dependent somatic withdrawal signs such as diarrhea and teeth chattering. This withdrawal-associated depression of ICSS can be fully reversed by subsequent administration of morphine or other MOR agonists. One interpretation of these findings is that morphine withdrawal produces anhedonic effects that are reflected in ICSS depression, suggesting that the abuse potential of morphine is related not only to its effectiveness to facilitate baseline ICSS, but also to reverse withdrawal-associated ICSS depression.

3. Neuroanatomy of morphine effects on ICSS

ICSS for abuse liability testing of drugs is usually maintained by electrical stimulation delivered either to the medial forebrain bundle at the level of the lateral hypothalamus or to the ventral tegmental area, and stimulation of both regions appears to drive excitatory inputs to mesolimbic dopamine neurons in the ventral tegmental area [4]. The neuroanatomical substrates mediating morphine effects on lateral hypothalamic/ventral tegmental area ICSS were examined in a study that evaluated ICSS after morphine microinjection into discrete brain areas [35]. Results indicated that ICSS rate-increasing and rate-decreasing effects are mediated by different neural sites. Specifically, ICSS facilitation was greatest after morphine microinjection into forebrain regions such as nucleus accumbens as well as into midbrain regions including the caudal hypothalamus/ventral tegmental area, a result consistent with other evidence to suggest that MOR agonists disinhibit mesolimbic dopamine neurons by inhibiting local GABAergic inputs to those neurons [36–38]. Conversely, ICSS depression was greatest after morphine microinjection into more caudal pontine mesencephalic regions. The role of different MOR populations in mediating morphine-induced ICSS facilitation and depression may also contribute to the observation described above that repeated morphine treatment often produces tolerance to ICSS depression but enhanced expression of ICSS facilitation. Specifically, repeated morphine desensitizes MOR opioid receptors more effectively in brainstem regions that mediate ICSS rate depression than in midbrain and forebrain regions that mediate ICSS facilitation, and this anatomically selective MOR desensitization may underlie selective tolerance to MOR-induced ICSS depression without tolerance to ICSS facilitation [39]. Moreover, repeated morphine also promotes intracellular signaling cascades (i.e. increased expression of ΔFosB) in forebrain regions such as nucleus accumbens that appear to produce sensitization rather than tolerance to morphine-induced rewarding effects [40]. Overall, these results suggest that MOR populations in different brain regions mediate morphine-induced ICSS facilitation and depression, respectively, and different responses of these MOR populations to repeated morphine exposure may simultaneously contribute to tolerance to ICSS depression and increased expression ICSS facilitation during repeated morphine treatment.

Although ICSS is usually maintained by stimulation delivered either to the medial forebrain bundle at the level of the lateral hypothalamus or to the ventral tegmental area, stimulation at

other sites can also maintain ICSS, and morphine effects may be influenced by the site of the stimulating electrode. For example, both morphine and cocaine facilitated ICSS maintained by electrical stimulation of either the medial forebrain bundle or the paraventricular nucleus; however, morphine was more effective than cocaine to facilitate ICSS of the paraventricular nucleus but less effective than cocaine to facilitate ICSS of the medial forebrain bundle [41]. As another example, morphine facilitated ICSS of the ventral tegmental area but depressed ICSS of the adjacent substantia nigra in rats [42].

4. Efficacy as a determinant of MOR agonist effects

MORs are seven-transmembrane domain receptors coupled to the $G_{\alpha i}$ subunit [43–46]. One of the first consequences of an agonist binding to the MOR is the exchange of GDP bound to $G_{\alpha i}$ for GTP [47]. The complexes resulting from this exchange activate signaling cascades that are ultimately responsible for MOR agonist effects. Efficacy is a measure of the maximum signaling achievable independent of dose, and measuring the amount of agonist-stimulated [^{35}S]GTPγS binding *in vitro* can serve as a functional read-out of MOR agonist efficacy. For example, morphine has intermediate efficacy to activate MORs; higher efficacy agonists (e.g. methadone) produce more [^{35}S]GTPγS binding in this assay, lower efficacy agonists (e.g. nalbuphine) produce less [^{35}S]GTPγS binding, and antagonists (e.g. naloxone and naltrexone) do not have efficacy and produce little or no signal under these conditions [48–52]. Based on these studies, some of the MOR ligands that have been examined in ICSS procedures can be ranked in terms of efficacy to stimulate [^{35}S]GTPγS binding as follows: methadone > fentanyl ≥ morphine ≥ oxycodone > buprenorphine > nalbuphine > NAQ (17-cyclopropylmethyl-3,14ß-dihydroxy-4,5α-epoxy-6α-[(3′-isoquinolyl) acetamido]morphinan) > naltrexone.

Efficacy is one factor that contributes to the behavioral effects of drugs in general, and MOR agonists specifically [53, 54]. Furthermore, the effects of MOR agonists in ICSS have demonstrated noticeable differences that depend upon efficacy, and these differences have been examined most extensively in male Sprague-Dawley rats. In these studies, there is very little evidence for facilitation of ICSS in opioid-naïve rats, regardless of MOR agonist efficacy [10, 30, 31, 55, 56]. However, depression of ICSS occurs in an efficacy-dependent manner: higher efficacy agonists produce the greatest depression in ICSS, and this depression diminishes until it is completely absent in MOR agonists with very low efficacy. Notably, ICSS depression induced by high-efficacy MOR agonists can be blocked by treatment with the MOR antagonist naltrexone at naltrexone doses that have no effect when administered alone. Morphine, as a MOR agonist with intermediate efficacy along the continuum, produces the more nuanced effect in opioid-naïve subjects detailed earlier: facilitation at later time points after an initial depression of ICSS has dissipated [10, 11]. This same pattern of behavior can be observed for oxycodone [56], which has similar efficacy to morphine. The MOR agonists with lower efficacy, such as NAQ and nalbuphine, while they do not produce any depression of ICSS, show some evidence of weak increases at isolated frequencies [30, 31, 55].

Treatments of repeated morphine administration produce changes in patterns of ICSS effects for other MOR agonists that are similar to what has been observed with morphine: tolerance

to initial ICSS depression and enhanced expression of abuse-related ICSS facilitation [11, 12, 14]. For example, although the high-efficacy agonists methadone and fentanyl produced only ICSS depression in opioid-naïve rats, repeated treatment with 3.2 or 18 mg/kg morphine unmasked facilitation for both drugs [30]. Furthermore, even very low-efficacy ligands like NAQ, which produced negligible effects in opioid-naïve rats, demonstrated robust facilitation after repeated treatment with 3.2 or 18 mg/kg morphine; however, repeated morphine does not unmask ICSS facilitation by MOR antagonists like naltrexone or naloxone [31]. Thus, MOR ligands require some efficacy at MORs to produce ICSS facilitation even after repeated morphine.

Less work has been conducted to examine changes in ICSS effects that occur after repeated treatment with other MOR agonists; however, as with morphine, repeated treatment with an intermediate dose of 1.0 mg/kg oxycodone also resulted in tolerance to ICSS depression and increased ICSS facilitation [56]. Overall, these results show ICSS facilitation by MOR agonists with a broad range of efficacies, which corresponds well to evidence from drug self-administration studies that also show reinforcing effects of MOR agonists with a broad range of efficacies [57–59].

5. Signaling bias as a determinant of MOR agonist effects

The high incidence of opioid abuse has stimulated efforts to discover new opioid compounds that might retain therapeutic effects of existing opioid analgesics but have fewer or less severe side effects, including lower abuse liability [1]. One intriguing category of drugs to emerge from this effort has been “biased” MOR agonists [60]. Many receptor targets are coupled to multiple intracellular signaling pathways, and it is now well established that different ligands for a given receptor can exert a selective or “biased” effect on subsets of signaling pathways coupled to that receptor. In the case of MORs, biased agonists have been identified that differentially activate MOR-coupled G-protein vs. ß-arrestin signaling pathways [61–64]. Biased MOR agonists that selectively activate G-protein signaling have attracted special attention because of evidence to suggest that G-protein signaling mediates analgesic effects but not some side effects of MOR agonists. Of particular relevance here is the claim by some that G-protein-biased MOR agonists may produce analgesic effects with reduced abuse liability; however, the only evidence to support this claim comes from a study in which the G-protein-biased MOR agonists TRV130 and PZM21 failed to produce a conditioned place preference under conditions in which morphine was effective [62].

Evidence from ICSS studies does not support the notion that G-protein-biased MOR agonists lack abuse liability. TRV130 (a.k.a. oliceridine) was among the first biased agonists to be discovered and advanced to clinical trials, and it is effective in both preclinical assays of antinociception and clinical assays of analgesia [61, 65]. However, in ICSS studies, TRV130 produced a profile of effects indistinguishable from that of abused MOR agonists like morphine [66]. Specifically, as with morphine (see Figure 2), TRV130 produced primarily dose-dependent ICSS depression in opioid-naïve rats, but repeated TRV130 administration produced tolerance to rate decreasing effects and enhanced expression of abuse-related ICSS facilitation. Moreover, TRV130 also produced ICSS facilitation in rats that had been treated repeatedly with morphine. These results were interpreted to suggest

that TRV130 has abuse liability similar to that of morphine and other MOR agonists, and other data provide additional evidence to suggest that G-protein-biased MOR agonists will retain abuse liability [67]. For example, TRV130 produced a typical morphine-like pattern of abuse-related subjective effects in humans (e.g. “Good Effects,” “High,” and “Liking”) [65], and studies using other preclinical assays of abuse potential (e.g. drug self-administration) did not observe significant differences between effects of TRV130 and abused opioid analgesics such as morphine [68, 69]. Overall, then, ICSS studies agree with the preponderance of other preclinical and clinical data in suggesting that G-protein biased MOR agonists will retain a morphine-like profile of abuse potential.

6. Opioid receptor selectivity as a determinant of opioid agonist effects

The shared effectiveness of MOR agonists to facilitate ICSS suggests that MOR activation is sufficient to facilitate ICSS. Pharmacological antagonism studies suggest that MOR receptor activation is also necessary for ICSS facilitation by morphine and some other MOR agonists. For example, MOR agonist-induced ICSS facilitation can be blocked by both the moderately MOR-selective and reversible antagonist naltrexone and by the more selective and irreversible MOR antagonist ß-funaltrexamine [55, 70].

ICSS has also been used to examine the effects of delta opioid receptor (DOR) and kappa opioid receptor (KOR) activation. DOR activation has produced conflicting results. Bilateral microinjection of the peptidic DOR agonist DPDPE into the nucleus accumbens facilitated ICSS in one study, although this effect was observed at only a single dose [71]. However, a role for MORs in DPDPE effects was not excluded in this study, and systemic administration of the nonpeptidic DOR agonists SNC80 and ARM390 failed to facilitate ICSS up to doses that produced ICSS depression and/or convulsions [22, 72]. Moreover, in contrast to results with repeated morphine, repeated SNC80 administration produced tolerance to SNC80induced ICSS depression but no emergence of ICSS facilitation [22]. Overall, these results support other studies to suggest reinforcing/rewarding effects of centrally administered peptidic DOR agonists [73] but not of systemically administered nonpeptidic DOR agonists like SNC80 [28, 74].

With regard to KOR agonists, one early study found that U69,593 produced only a dose-dependent depression of ICSS, and this ICSS depression could be blocked by pretreatment with a kappa antagonist that had no effect on its own [75]. Other studies have confirmed this finding of ICSS depression with U69,593 and extended it to other selective KOR agonists including U50,488, spiradoline, nalfurafine, and salvinorin A [72, 76–81]. The effectiveness of kappa agonists to decrease ICSS has been linked to a role for KORs in inhibiting activity of mesolimbic dopamine neurons [82]; however, the failure of KOR antagonists to facilitate ICSS suggests that basal tone at KORs is low and blocking these receptors does not disinhibit activity of mesolimbic dopamine neurons. In contrast to the effects of repeated treatment with MOR agonists, repeated treatment with the KOR agonist salvinorin A once daily for eight days produced repeatable effects during the hour after its administration with no evidence for either tolerance to the ICSS depression or increased expression of ICSS facilitation [24]. Intriguingly, 24 hr after daily salvinorin A treatments, ICSS facilitation was occasionally observed, suggesting that repeated exposure to and withdrawal from KOR

agonists may produce ICSS facilitation in a manner reciprocal to the ICSS depression observed during withdrawal from MOR agonists.

Side effects of KOR agonists have long been known to limit their use for potential clinical applications, and ICSS depression may serve as a preclinical manifestation of kappa agonist effects such as sedation and dysphoria that are problematic clinically. One strategy to reduce these side effects has been to develop KOR agonists that do not distribute well across the blood-brain barrier and might therefore produce reduced centrally mediated effects after peripheral administration. Consistent with this idea, the peripherally restricted KOR agonists ffir (a tetrapeptide) and ICI204448 produced antinociception in rats at doses that did not facilitate or depress ICSS; however, as with other KOR agonists, higher doses of these compounds did depress ICSS [81]. A second strategy has been to develop biased KOR agonists to preferentially activate G-protein-signaling pathways hypothesized to mediate therapeutic effects such as antinociception more than ß-arrestin-signaling pathways hypothesized to mediate undesirable effects such as ICSS depression. In support of this approach, the G-protein signaling biased KOR agonist triazole 1.1 produced antinociception in rats at a dose that did not depress or facilitate ICSS [76]. Thus, neither peripherally restricted nor G-protein-biased KOR agonists have produced evidence for abuse-related ICSS facilitation, although high doses of these compounds may produce ICSS depression.

The nociception/orphanin FQ receptor is also sometimes included as an opioid receptor because of the degree of its homology to the three major types of opioid receptor; however, an agonist for this receptor (R0 64–6198) also failed to facilitate ICSS up to doses that disrupted responding [83]. Overall, then, the MOR has been the only opioid receptor found to consistently mediate ICSS facilitation.

7. Species, strain, and sex as determinants of MOR agonist effects

Opioid effects on ICSS have been examined in both rats and mice, and strain appears to be an important determinant of MOR agonist effects in both species. In rats, MOR agonist effects have not been directly compared across strains, but several different strains have been used, and strain differences appear likely. As noted above, acute morphine administration in opioid-naïve male Sprague-Dawley rats has generally been found to produce initial ICSS depression that may be followed hours later by delayed ICSS facilitation; however, repeated treatment produces tolerance to ICSS depression along with earlier and enhanced expression of ICSS facilitation. Similar results have been reported in male Long-Evans rats [84]. In male Wistar rats, acute morphine doses also produced initial ICSS depression followed by delayed ICSS facilitation in opioid-naïve rats; however, in contrast to results in Sprague-Dawley or Long-Evans rats, regimens of repeated morphine administration in Wistar rats failed to produce tolerance to ICSS depression or earlier expression of ICSS facilitation [85]. Conversely, morphine and other MOR agonists have produced potent and rapid-onset ICSS facilitation even in opioid-naïve F344 male rats [86–88].

Strain differences in opioid effects have been more directly evaluated in mice. For example, a direct comparison of morphine effects in male C57BL/6J and DBA/2J mice found that morphine dose-dependently facilitated ICSS in C57BL/6J mice, but the same morphine

doses produced only ICSS depression in DBA/2J mice [89]. This strain difference in morphine effects did not generalize to amphetamine, which facilitated ICSS in both strains. Moreover, ICSS results paralleled effectiveness of morphine to maintain drug self-administration in C57BL/6J but not in DBA/2J mice, and other groups have also reported ICSS facilitation by morphine in C57BL/6J mice [90]. The authors of the strain-difference study speculated that differential morphine effects may be related to strain differences in KOR receptor signaling, with higher KOR density in nucleus accumbens of DBA/2J mice possibly resulting in higher KOR-mediated ICSS depressant effects of morphine in this strain [89]. Morphine effects have also been reported to vary in mice with genetic mutations to knockout the MOR or the dopamine D2 receptor. The MOR knockout was accomplished in mice on a C57/129 background, and morphine produced ICSS depression in the wildtypes and heterozygotes but did not significantly alter ICSS in the knockouts (sex not specified) [91, 92]. Thus, in these mice, morphine produced a MOR-mediated ICSS depression. The dopamine D2 receptor knockout was accomplished in mice backcrossed to C57BL/6J mice, and morphine effects were tested in males [93]. Morphine facilitated ICSS in the wildtypes, but it produced mixed ICSS facilitation and depression in the heterozygotes and only ICSS depression in the knockouts. Again, amphetamine facilitated ICSS in all three genotypes. Effects of repeated morphine have not been examined in mice, so it is unknown if the ICSS depression observed in some strains might decline and reveal ICSS facilitation.

As with most preclinical behavioral pharmacology research, most studies of opioid effects on ICSS have been conducted in male subjects. However, three studies have compared morphine effects in male and female rats [14, 94, 95]. The first of these three studies found that baseline ICSS parameters did not differ between male and female Sprague-Dawley rats or in females at different stages of the estrous cycle [95]. Rats were opioid-naïve at the start of testing, and morphine at doses up to 5.6 mg/kg only depressed ICSS in both sexes, whereas cocaine and amphetamine facilitated ICSS in both sexes. A second study using male and female Sprague-Dawley rats evaluated effects of repeated daily morphine administration for 7 days [14]. Upon initial administration, when rats were opioid-naïve, morphine again produced only dose-dependent ICSS depression in both sexes; however, in this study, there was a significant interaction between sex and morphine dose, and 3.2 mg/kg morphine tended to facilitate ICSS in females but depress ICSS in males. Seven days of repeated treatment with 3.2 mg/kg/day morphine increased expression of morphine-induced ICSS facilitation in both males and females and eliminated the sex difference in morphine effects. The final study used male and female Long-Evans rats with different postnatal experiences (maternal separation vs. no handling) but no prior exposure to opioid agonists [94]. Morphine at doses up to 3.0 mg/kg failed to alter ICSS in either sex, and there were no sex differences in morphine effects. Taken together, these studies provide little evidence for sex differences in morphine effects on ICSS in opioid-naïve rats. In the one study that did observe a sex difference [14], effects of an intermediate morphine dose (3.2 mg/kg) were different in females and males, with slight ICSS facilitation in females and slight ICSS depression in males; however, repeated morphine increased ICSS facilitation by this morphine dose in both sexes and eliminated the sex difference.

8. Pain states as a determinant of MOR agonist effects

The role of pain as a modulator of MOR agonist abuse potential has been an issue of particular interest given the clinical risk of iatrogenic addiction (i.e. addiction that develops during the use of opioids for medical treatment). Clinical data published in the 1980s were interpreted to suggest that risk of addiction was low when opioid use occurred in the context of pain treatment [96, 97], and this perception likely contributed to the dramatic escalation in clinical opioid use that occurred through the 1990s and up to the present [98, 99]. However, more recent evidence suggests that rates of iatrogenic opioid addiction may be high [100, 101], and as noted above, other recent data indicate that clinically prescribed opioid exposure for as few as 5 days is associated with increased risk of long-term opioid use [17]. These findings suggest that opioids retain considerable abuse liability in pain patients, and this concern has triggered the implementation of more restrictive guidelines for opioid prescriptions [102].

In one set of ICSS studies to address the role of pain states as a determinant of opioid abuse potential, opioid-induced ICSS facilitation was evaluated in male F344 rats with a spinal nerve ligation (SNL) model of neuropathic pain [86, 87]. SNL did not alter baseline ICSS or cocaine-induced ICSS facilitation; however, SNL decreased the potency or effectiveness of a wide range of MOR agonists to produce ICSS facilitation. Thus, these studies suggested that the SNL model of neuropathic pain reduced opioid abuse potential, and this group similarly reported that SNL reduced the potency or effectiveness of MOR agonists to maintain drug self-administration in rats [103].

In contrast to these findings with the SNL pain model, other pain models have produced no change in ICSS facilitation by morphine. In one study, morphine dose-effect curves were determined in male Sprague-Dawley rats before and after repeated daily morphine doses administered either alone or in combination with an intraperitoneal injection of dilute lactic acid (IP acid) as a repeated visceral pain stimulus [12]. As discussed above, morphine initially produces primarily ICSS depression in male Sprague-Dawley rats, but after repeated administration, tolerance develops to ICSS depression, and morphine-induced ICSS facilitation becomes increasingly prominent. The co-administration of IP acid did not alter this trajectory of increasing morphine-induced ICSS facilitation. In a second study, effects of repeated morphine were evaluated in male and female Sprague-Dawley rats treated with the cancer chemotherapy drug paclitaxel to model chemotherapy-induced neuropathic pain [14]. Again, the trajectory of increasing morphine-induced ICSS facilitation was similar in paclitaxel-treated rats and saline-treated controls. Taken together, these results suggest that repeated morphine exposure can increase expression of abuse-related effects of morphine, and neither a repeated visceral pain state nor a sustained chemotherapy-induced neuropathic pain state were sufficient to protect against this effect of repeated morphine. The effects of these two pain manipulations (repeated intraperitoneal acid administration, paclitaxel treatment) on opioid self-administration have not been examined; however, previous studies have shown increased morphine self-administration during an acute electrical pain stimulus [104], and adjuvant-induced models of arthritis pain decreased intravenous morphine self-administration [105] but increased oral fentanyl self-administration [106, 107].

9. Future directions

ICSS is one type of experimental procedure that can be used to evaluate the abuse potential drugs, and it has been used for decades to investigate determinants of opioid abuse potential. One of the most important contributions of ICSS to research on opioid abuse potential has been the finding that MOR agonists often fail to produce evidence for abuse-related ICSS facilitation in opioid-naïve subjects, but repeated morphine exposure for as little as a few days can rapidly increase expression of abuse-related effects. These findings support current clinical efforts to limit patient exposure to opioid analgesics during pain treatment. ICSS studies also complement results from other preclinical drug self-administration procedures in suggesting that even low-efficacy and G-protein biased MOR agonists have abuse potential, and that both trait and state variables of the experimental subject can influence opioid abuse potential.

Future studies with ICSS could focus on a range of topics, and three will be mentioned here. First, one important goal of future research will be to investigate factors that underlie the increase in abuse potential produced by initial opioid exposure and to investigate strategies to prevent it. As one simple example, we reported that increases in ICSS facilitation produced by repeated morphine administration were dependent on the dose and duration of repeated morphine, and importantly, it was possible to produce sustained antinociception with a relatively low morphine dose that triggered little increase in abuse-related effects [12]. Thus, one strategy to minimize increasing opioid abuse potential during initial opioid exposure for pain treatment would be to use the lowest effective analgesic dose for the shortest period of time. This is precisely the sort of strategy being recommended by new opioid-use guidelines [102]. Moreover, if opioid-induced increases in abuse potential are dose dependent, they may also be dependent on the efficacy of the MOR agonist. It is well established that even low-efficacy MOR agonists like nalbuphine or NAQ can produce abuse-related ICSS facilitation after repeated administration of the higher efficacy MOR agonist morphine [30, 31]; however, the effects of repeated treatment with these low-efficacy ligands themselves on ICSS have not been examined. It is possible that repeated treatment with low-efficacy MOR agonists may be sufficient to produce pain relief without triggering increases in ICSS facilitation and abuse potential.

A second goal of future studies will be to examine abuse-related effects of novel opioids being either developed as candidate analgesics with reduced abuse potential or identified as designer opioids being synthesized and distributed for illicit use. As noted above, G-protein biased MOR agonists such as TRV130 are being actively developed and evaluated as candidate analgesics, and some have argued that these drugs might also have reduced abuse potential; however, ICSS studies were the first to indicate that TRV130 retains morphine-like abuse potential [66], and more recent studies using other procedures have supported this conclusion [68]. Many other novel opioids are being developed with a variety of distinguishing pharmacokinetic or pharmacodynamic characteristics designed to retain analgesic effects while reducing abuse potential [108–110], and ICSS can be used to evaluate the degree to which this goal is met. Other novel opioids, such as the fentanyl analogs, are also emerging as drugs available for illicit use, and abuse-potential assessment of these drugs will play an important role in guiding their control by regulatory agencies

[111]. An important consideration in studies with novel opioids will be not only the degree to which they produce abuse-related ICSS facilitation after their own administration, but also the degree to which their repeated delivery increases ICSS facilitation by other abused MOR agonists.

A final and underutilized application of ICSS procedures will be to examine candidate treatments for opioid use disorder. Specifically, candidate treatments for opioid use disorder could be evaluated for their effectiveness to either (a) block MOR agonist-induced ICSS facilitation in non-dependent or formerly dependent subjects, or (b) prevent/reverse withdrawalinduced ICSS depression in opioid-dependent subjects. The first type of approach is exemplified by clinically approved antagonist medications such as naltrexone, and consistent with its clinical effectiveness, we found that naltrexone maintenance in rats (achieved by continuous delivery with an osmotic minipump) produced a dose-dependent blockade of morphine effects on ICSS [112]. The second type of approach is exemplified by clinically approved agonist medications such as methadone, and again consistent with its clinical effectiveness in opioid-dependent patients, we found that methadone and other MOR agonists reversed withdrawal-associated ICSS depression in opioid-dependent rats [30]. Other MOR ligands could also be systematically evaluated for their effects on these endpoints in rats with graded levels of opioid dependence, and perhaps of greater interest, these approaches could also be used to examine non-opioid treatments that target neural systems hypothesized to play key roles in opioid relapse [113, 114].

Acknowledgements

This work was supported by the National Institutes of Health Grant R01NS070715.

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Highlights

- ICSS has been useful to investigate determinants of opioid abuse potential
- ICSS reveals rapid emergence of abuse potential during early opioid exposure
- Low-efficacy and G-protein-biased MOR agonists have abuse potential
- Test-subject state/trait variables can affect expression of opioid abuse potential
- ICSS can play a key role in research responding to the opioid abuse crisis

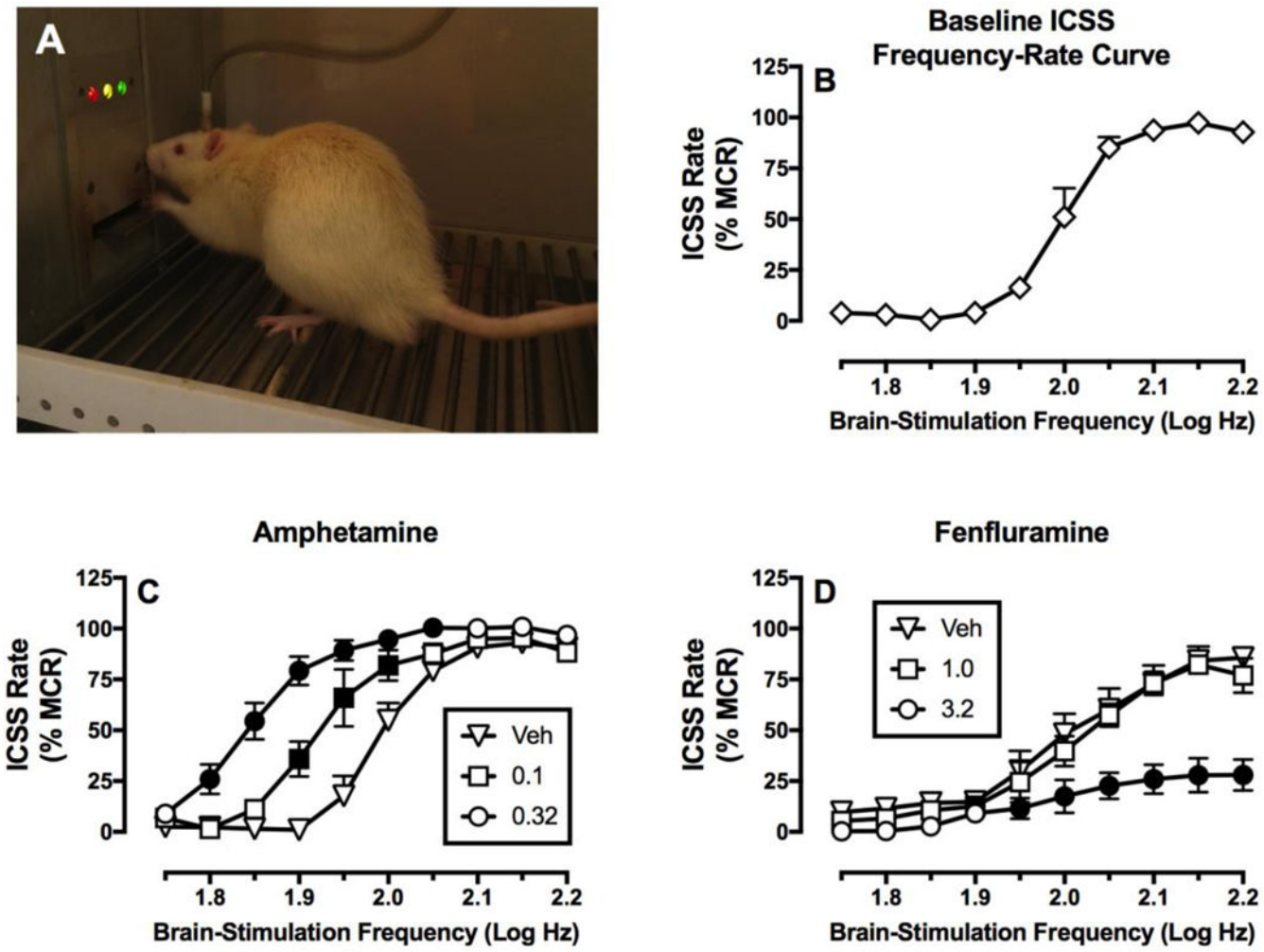

Figure 1. Overview of ICSS procedure.

Panel A shows a male Sprague-Dawley rat in an operant conditioning chamber pressing a lever for electrical brain stimulation. Stimulation is delivered via a microelectrode that is implanted in the medial forebrain bundle and attached by a cable to an ICSS stimulator located outside the frame of the photograph. Panel B-D show representative data collected using a "frequency-rate" ICSS procedure, in which brain-stimulation frequency is varied during daily behavioral sessions, and rates of responding are monitored during availability of each frequency. Panel B shows representative baseline data, whereas Panels C and D show effects of injection with Vehicle (Veh) or various doses of amphetamine or fenfluramine, respectively. Drugs with abuse liability (e.g. amphetamine) typically produce leftward/upward shifts in ICSS frequency-rate curves across some range of doses, whereas drugs without abuse liability (e.g. fenfluramine) typically fail to facilitate ICSS at any doses up to those that produce rightward/downward shifts in ICSS frequency-rate curves. Abscissae: Log brain-stimulation frequency in Hz. Ordinates: ICSS response rate expressed as % Maximum Control Rate (%MCR), a transformation that normalizes data in each rat on each test day to maximum rates during baseline sessions. Filled points in C and D show rates

significantly different from those after Vehicle (Veh) administration ($p<0.05$). All points show mean ± SEM from 6 rats. Data adapted from [6].

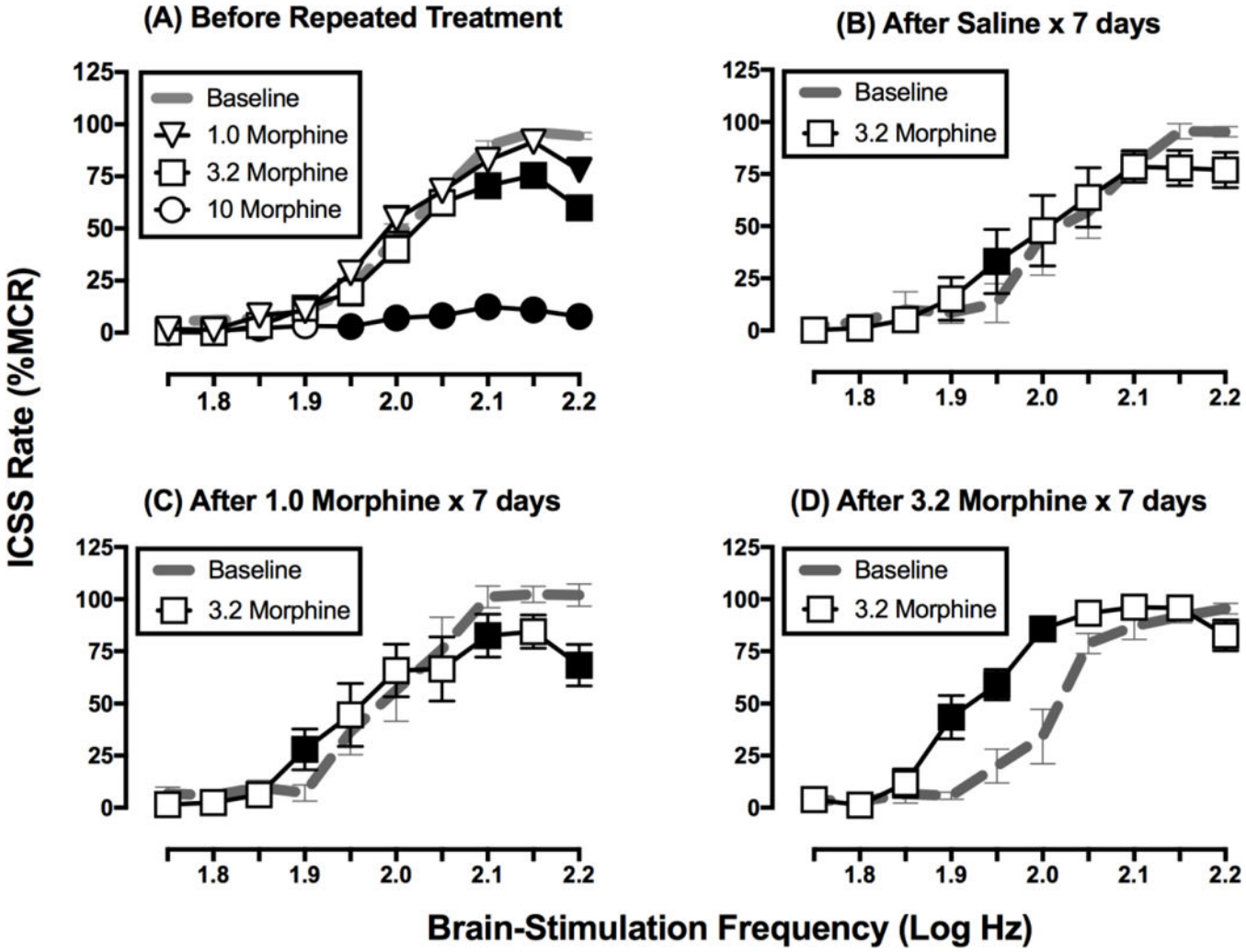

Figure 2. Repeated morphine exposure increases expression of morphine-induced ICSS facilitation.

Abscissae: Log brain-stimulation frequency in Hz. Ordinates: ICSS response rate expressed as % Maximum Control Rate (%MCR). Panel A shows data from 20 drug-naïve male Sprague-Dawley rats. These rats were subsequently divided into three groups that received repeated daily treatment with saline (B, N=6), 1.0 mg/kg/day morphine (C, N=7), or 3.2 mg/kg/day morphine (D, N=7). All data show mean ± SEM, and filled points indicate significantly different from Baseline ($p<0.05$). Data adapted from [12].

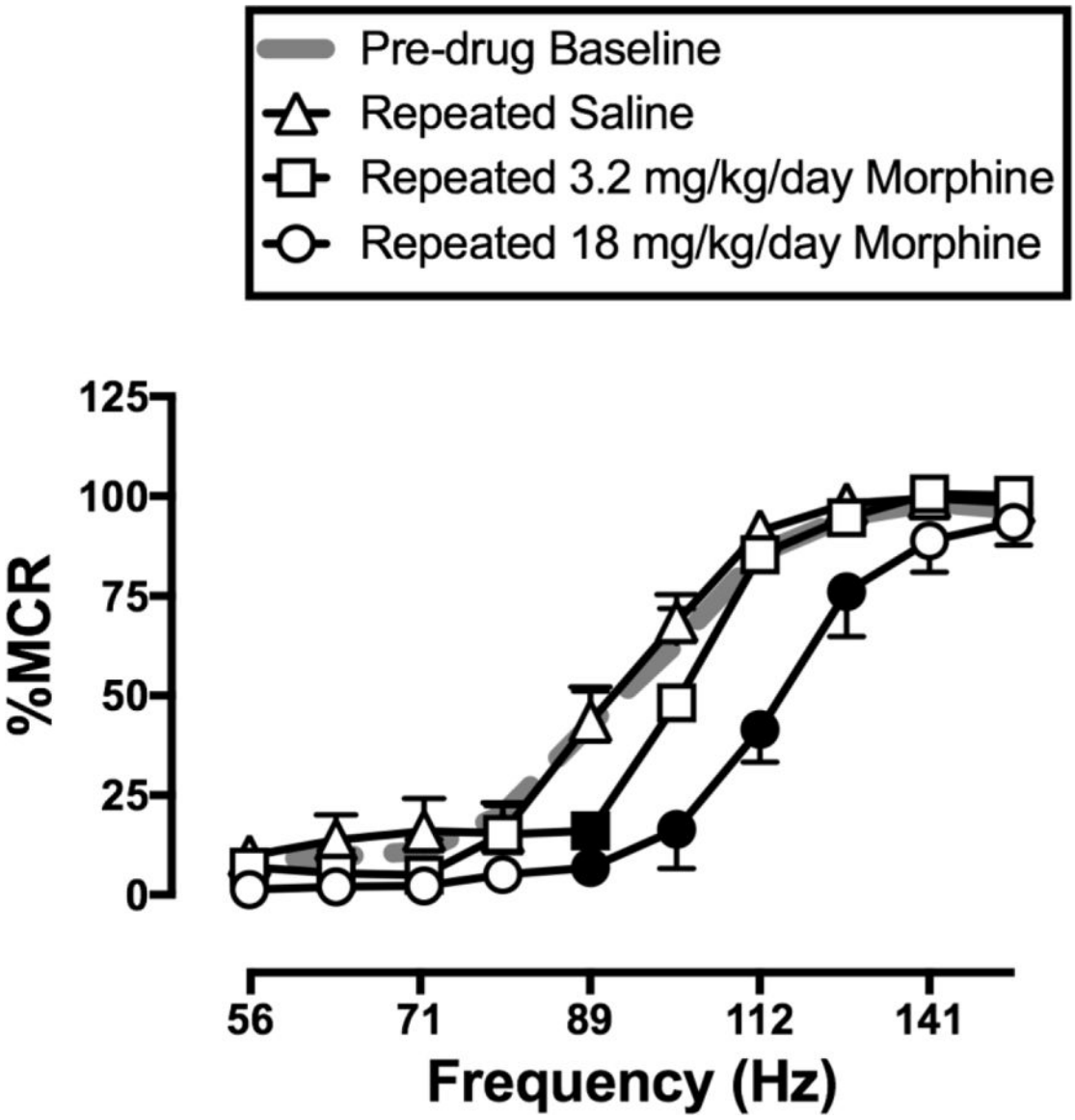

Figure 3. Morphine withdrawal depresses ICSS.

Abscissae: Log brain-stimulation frequency in Hz. Ordinates: ICSS response rate expressed as % Maximum Control Rate (%MCR). Rats (N=5) were treated sequentially for at least one week with daily treatments of saline, then with 3.2 mg/kg/day morphine, and lastly with 18 mg/kg/day morphine. ICSS frequency-rate curves were collected before repeated treatment (Pre-drug Baseline) and approximately 23 hr after daily injections on selected test days. Thus, results show effects of 23-hr withdrawal from the designated chronic treatment. All data show mean ± SEM, and filled points indicate significantly different from Pre-drug Baseline ($p<0.05$). Data adapted from [31].