EXOGENOUSLY administered opioids display marked interindividual differences with respect to their intended (analgesia) and unwanted (e.g., respiratory depression, nausea and vomiting) pharmacologic effects. In addition to the well-documented effects of age or development and genetic background, the contribution of gender and hormonal status as factors in opioid potency is becoming increasingly appreciated. We review recent findings on the interaction of sex and opioid analgesic potency and discuss possible mechanisms. Although most of the literature on sex differences in opioid analgesia comes from work with rodents, the available human data also indicate the presence of sex differences. Because opioids exert their analgesic effects through $\mu$-, $\delta$-, and $\kappa$-opioid receptor (OR) subtypes, each with a unique pharmacology and role in pain control, each OR subtype is considered separately.

In general, progress in the area has been slow. This may reflect the overwhelming use of male subjects to circumvent controlling for estrous or menstrual status or the failure of some researchers to examine their data for sex differences. The lack of consistent sex differences in opioid analgesia may reflect differences in the methodology (e.g., species, strain and age of subjects, particular nociceptive assay employed, quantification of analgesia) employed by each laboratory. It is beyond the scope of this paper to detail comprehensive methodologic details of all the reports cited in this article. We provide details of some studies in which apparently contradictory or complimentary findings necessitate elaboration. Nonetheless, findings from the increasing number of well-controlled animal and human studies directly examining the issue of sex in the potency of opioids show that patient sex may impact on the clinical efficacy of opioids for pain.

Animal Studies

$\mu$-Opioid Receptor Agonists

In rats and mice, the majority of studies report that the potency (i.e., $ED_{50}$ values) and efficacy (i.e., drug-induced increase in pain response latency) of morphine administered systemically are higher in male than in female animals$^{2-13}$ (table 1). The enhanced sensitivity to morphine analgesia displayed by male animals has been documented with several pain assays, including those assessing thermal (hot-plate tests$^{2,6,9,10,13}$), somatic (tail-flick-withdrawal tests$^{2,3,5,14}$), chemical (abdominal writhing after acetic acid$^2$), visceral (hypertonic saline$^4$), and electric shock (jump test$^{14}$) nociception. Studies utilizing central routes of administration suggest that sex differences in opioid analgesia are probably mediated, at
least in part, by differential central nervous system (CNS) sensitivity to opioids. Morphine ED$_{50}$ values are smaller in males after injections of morphine or the $\mu$-OR selective agonist D-Ala$^2$-MePhe$^4$-Gly-$\alpha$-ol$^5$-enkephalin (DAMGO), via the intracerebroventricular (ICV) route in rats$^{14,15}$ and mice.$^{16,17}$ Morphine injections into supraspinal CNS regions critically involved in descending opioid pain inhibition, such as the and rostral ventromedial medulla,$^{18}$ also

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**Table 1. Studies Regarding Sex Differences in Opioid Analgesia in Various Rodent Populations**

<table>
<thead>
<tr>
<th>Strain*</th>
<th>Opioid†</th>
<th>Receptor‡</th>
<th>Route§</th>
<th>Assay</th>
<th>Results#</th>
<th>Reference</th>
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<tr>
<td>Rat</td>
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<tr>
<td>SD</td>
<td>Morphine</td>
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<td>iRVM</td>
<td>TW</td>
<td>M &gt; F‡‡</td>
<td>20</td>
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</table>

*SD = Sprague-Dawley; W = Wistar; SW = Swiss-Webster; HA/LA = two lines bidirectionally selected (outbred stock) for high (HA) and low (LA) swim stress-induced analgesia; NR = not reported; Deer = insular wild deer mice; Inbred¹ – A, BALB/c, C3H/He, DBA/2, LP, SJL; Inbred² – CBA; Inbred³ – AKR, C57BL/6, SWR.  
†DAMGO = (D-Ala$^2$-MePhe$^4$-Gly-$\alpha$-ol$^5$)-enkephalin; DSLET = (L-Ser$^2$, Leu$^\alpha$)-enkephalin-Thr$^\beta$; DPDPE = (D-Pen$^2$, D-Pen$^5$)-enkephalin; Deltorphin = (L-Ala$^2$, Glu$^\alpha$)-deltorphin.  
‡Opioid receptor subtype selectivity.  
§s.c. = subcutaneous; i.p. = intraperitoneal; i.c.v. = intracerebroventricular; iPAG = intraperireaqueductal gray; iRVM = intrarostroventral medulla.  
||AC = abdominal constriction test; ES = electric shock jump (or flinch) test; HP = hot-plate test; TF = tail-flick (radiant heat) test; TW = tail withdrawal (hot water) test.  
#F > M = females more sensitive than males; M > F = males more sensitive than females; No = no significant sex differences.  
**No sex differences in radioligand binding for this receptor in hypothalamus or cortex.  
††Sex difference was dose-dependent.  
†††No sex differences in morphine pharmacokinetic parameters.  
§§No significant difference, but trend toward F > M.  
|||Sex difference was time-dependent.  
##No significant difference, but trend toward M > F‡‡[].  
###Analgesia increased in aging males, but decreased in aging females.  
†††Morphine also decreased locomotion in males.  
††††Brain morphine levels greater in males.  
§§§Greater antagonism of analgesia in males by antiopeptide Tyr-MIF-1.  
||||Greater antagonism of analgesia in males by neuropeptide FF.  
###Greater antagonism of analgesia in males by N-methyl-D-aspartate (NMDA) receptor antagonist MK-801.  
****Opiate-induced alterations in activity greater in males.  
††††Analgesia blocked by NMDA receptor antagonist MK-801 in males.
produce greater analgesia in male relative to female rats.\textsuperscript{19,20} Despite the greater sensitivity to analgesia in males by morphine and DAMGO, which are prototypic $\mu$-OR agonists, it is not possible to generalize about sex differences in $\mu$-OR analgesia because important exceptions are observed. Bartok and Craft observed no analgesic differences between male and female rats on either the hot-plate or tail-withdrawal assay after systemic administration of fentanyl or buprenorphine.\textsuperscript{21} Furthermore, although male rats displayed significantly greater DAMGO analgesic magnitude on the tail-flick test relative to female rats after ICV injections,\textsuperscript{15} there were no sex differences in ED$_{50}$ values derived from the DAMGO dose–response curve, nor were there sex differences in either magnitude or ED$_{50}$ values on the jump test. Therefore, sex differences in $\mu$-opioid analgesia may depend on the specific agent tested, the route of administration, the nociceptive assay used, and the method used to quantify analgesia.

The magnitude and direction of sex differences in morphine analgesia appears to vary with other intrinsic factors, such as genotype. For example, male Sprague–Dawley and Wistar–Furth rats displayed greater morphine analgesia than their female counterparts after systemic administration, and sex-related potency differences varied in magnitude between these strains.\textsuperscript{12} In mice, the presence, magnitude, and direction of sex differences in morphine analgesia after ICV administration differed among 11 genetically distinct inbred strains.\textsuperscript{17} The influence of genotype on sex differences is not limited to morphine analgesia. In a study examining central DAMGO analgesia in mice selected from Swiss–Webster stock for high and low stress-induced analgesia, high stress-induced analgesia male mice, but not low stress-induced analgesia male mice, displayed greater analgesic potency than their female counterparts.\textsuperscript{16} Age has also been shown to interact with sex in the modulation of morphine analgesia. Whereas there is an age-related increase of peak and total (area under the curve) morphine analgesia in male rats, female rats display an age-related decrease, although at a low dose females may actually show an enhanced response.\textsuperscript{3} Finally, sex differences fluctuate throughout the day in mice and are maximal during the dark period, during which opioid sensitivity is greater in males.\textsuperscript{6}

**Morphine Tolerance.** One consequence of repeated morphine exposure is a decrease in its analgesic potency (i.e., tolerance). Differences between sex have been observed in the magnitude and potency of morphine toler-
ance. In one study, for example, there was a significant attenuation of morphine analgesia on the hot-plate and jump tests in male rats treated with morphine for 14 days. Females, in contrast, displayed no tolerance on the jump test and less tolerance on the hot-plate test. In a recent report, male rats were more tolerant than females to morphine analgesia on the hot-plate test after twice-daily or once-weekly morphine injections. Despite the greater loss of analgesia in males, recovery of morphine analgesic potency after discontinuation of chronic treatment was more rapid in this sex. A similar pattern is observed in the tail-withdrawal test, where repeated administration of morphine at weekly intervals for 3 weeks or twice daily for 7 days resulted in more rapid tolerance in males, as determined by total morphine analgesia (area under the curve) or morphine ED50 values, respectively. The magnitude of tolerance on the tail-flick test in neonate rats, however, is not affected by sex. Thus, the ontologic development of sex differences in morphine tolerance on the tail-withdrawal–flick test in rats remains unknown.

In mice, sex differences in morphine tolerance on the tail-withdrawal test are observed, but the direction of this difference is contrary to that seen with rats. Repeated subcutaneous morphine injections daily for 3 or 7 days produced tolerance in both sexes, but there was a significantly greater rightward shift in the morphine dose-response curve and increased ED50 value for females. For both sexes, the magnitude of tolerance after 7 days was larger than that observed after 3 days, but the male–female difference was similar. This suggests that sex differences in morphine tolerance in mice may develop quickly, but then progressively slows, even as the magnitude of tolerance in both sexes increases.

**κ- and δ-Opioid Receptor Agonists**

Sex differences in the analgesic effects of opioids acting at the κ- and δ-OR types have also been reported (table 1). Similar to μ-OR analgesia, sex differences may be assay-, dose-, or time-dependent. After administration of the κ-OR-selective opioid U69,593 in rats, significant sex differences were noted in latency to peak analgesia (females, 5–15 min; males, 30 min) after drug administration on the tail-withdrawal test but not the hot-plate test. In the same study, the κ-OR agonist brendazocine produced more analgesia in females compared with males at some dose and time points on both assays. Sex differences in the magnitude of κ-OR analgesia are also observed in mice, with males displaying greater analgesia than females on the hot-plate after the κ-OR selective agonist U-50,488H.

There were no sex differences in the δ-OR analgesia of [δ-Ser2,Leu5]enkephalin-Thr6 (DSLET), an enkephalin-containing ligand, on the tail-flick or hot-plate test. However, distinct δ-OR subtypes, δ1 and δ2, have subsequently been identified. Their selective agonists, [δ-Pen2,δ-Pen5]enkephalin (DPDPE) and deltorphin, respectively, produced analgesia in rats that displayed sex differences at some doses on the hot-plate test but not the tail-flick test, with significantly less analgesia in females than in males. Additionally, the time to peak DPDPE analgesia also differed between males (15–30 min postinjection) and females (5 min postinjection).

**Mechanisms of Sex Differences in Opioid Analgesia**

The mechanism or mechanisms underlying sex differences in opioid analgesia remains elusive. The larger concentration of morphine in the brain of male mice relative to female mice after systemic injections suggests simple sex differences in drug disposition. However, in rats, there are no differences in morphine serum levels between sexes at times corresponding to the drug’s peak analgesic effect. Additionally, the larger magnitude of analgesia observed in male mice and rats relative to female counterparts after the administration of opioids directly into the CNS makes sex differences in opioid pharmacokinetics an unlikely explanation of sex differences in opioid analgesia. Sex differences in opioid analgesia are also not likely related to differences in supraspinal OR density because there are no differences between male and female rats in brain μ- or δ-OR populations. In mice, studies of sex-related differences in brain OR populations yield conflicting results; one study reported increased levels in males, another reported no differences between sexes. Finally, the relation between OR density and sex differences in analgesia is questioned by the report that male mice display increased sensitivity to morphine analgesia relative to females after chronic opioid antagonist treatment with naltrexone despite no effect of sex on the degree of OR upregulation.

Sex differences in opioid analgesia may also result from sex differences of the endogenous neurochemical systems that facilitate drug reward systems. For example, the endogenous opioid peptides leu- and met-enkephalin can also affect morphine potency, and sex differences in their density has been shown in the rat. In this regard, it is worth noting that the activity of endogenous opioid peptides is terminated by several proteolytic enzymes, and that the antinociceptive effects of enkephalinase inhibition is larger in males.

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Table 2. Effect of Gonadal and Hormonal Status on Opioid Analgesia

| Opioid | Receptor† | Route‡ | Assay§ | Gonadal/Hormonal Manipulation|| Recovery/Treatment‡‡ | Results** | Reference |
|--------|-----------|--------|--------|--------------------------------|-------------------|-------------|----------|
| DAMGO  | µ         | i.c.v.  | ES     | O VX/TX                        | 5.5 wk            | O VX ↓     | 15       |
| DAMGO  | µ         | i.c.v.  | TF     | O VX/TX                        | 5.5 wk            | No††       | 15       |
| Morphine | µ      | s.c.    | AC     | O VX                           | 3 wk              | No         | 4        |
| Morphine | µ      | i.c.v.  | ES     | O VX/TX, EP                    | ≥ 5 wk            | O VX ↓ §§; P > E, O VX | 14       |
| Morphine | µ      | s.c.    | HP     | O VX                           | 4 wk              | O VX ↑ , TX ↓ §§## | 19       |
| Morphine | µ      | s.c.    | HP     | O VX                           | 2 wk              | No         | 2        |
| Morphine | µ      | s.c.    | HP     | O VX/ET                        | 3 wk/24 d         | ET ↑ #***  | 38       |
| Morphine | µ      | s.c.    | TF     | O VX/TX                        | ≥ 12 wk           | O VX ↑ , TX, No | 3        |
| Morphine | µ      | s.c.    | TF     | O VX, ET                       | 1 wk              | No***      | 12       |
| Morphine | µ      | s.c.    | TF     | ET, TP                         | 0.5, 4 h          | ET ↓, TP (0.5 h ↑, 4 h ↓) | 40       |
| Morphine | µ      | s.c.    | TF     | TX                            | 1 wk              | TX ↑       | 40       |
| Morphine | µ      | s.c.    | TF     | TX, TP                        | ≥ 1 wk            | No         | 41       |
| Morphine | µ      | s.c.    | TF     | O VX, ET, TP                   | 1 wk              | O VX ↓ †††‡‡‡ | 35       |
| Morphine | µ      | s.c.    | TF     | TX                            | ≥ 5 d             | No §§§     | 5*       |
| Morphine | µ      | i.c.v.  | TF     | O VX/TX                        | ≥ 5 wk            | O VX ↓ §§; P > E, O VX | 14       |
| Morphine | µ      | i.PAG   | TF     | O VX/TX                        | 4 wk              | O VX ↑ §§## | 19       |
| Sufentanil | μ   | i.t.    | ES     | ET†                           | 1.5 wk            | No         | 39       |
| DSLET  | δ1/2     | i.c.v.  | ES     | O VX/TX                        | 5.5 wk            | TX ↓, O VX ↓ # | 15       |
| DSLET  | δ1/2     | i.c.v.  | TF     | O VX/TX                        | 5.5 wk            | TX ↓ #     | 15       |
| U50,488H | κ     | i.t.    | ES     | ET†                           | 1.5 wk            | ET ↑       | 39       |

* All studies performed in rats except where noted (mouse).
† Opioid receptor subtype selectivity.
‡ s.c. = subcutaneous; i.c.v. = intracerebroventricular; i.PAG = intraperiventricu-dal gray; i.t. = intrathecal.
§ AC = abdominal constriction test; ES = electric shock jump (or flinch) test; HP = hot-plate test; TF = tail-flick (radiant heat) test; TW = tail withdrawal (hot water) test.
|| O VX = ovariectomy; TX = castration; EP = estrous phase considered; ET = estrogen (17β-estradiol or progesterone) treatment; TP = testosterone treatment.
# Recovery = latency between O VX/TX and testing; treatment = duration of ET/TP treatment.
** No = no effect of gonadectomy, estrous phase, or hormonal treatment; O VX ↓ = ovariectomy decreased analgesia; O VX ↑ = ovariectomy increased analgesia; TX ↓ = castration decreased analgesia; TX ↑ = castration increased analgesia; ET ↓ = estrogen treatment decreased analgesia; ET ↑ = estrogen treatment increased analgesia; P = proestrous; E = estrus; D = diestrus (including metestrus).
†† Hormone-simulated pregnancy.
‡‡ Greater analgesia in males after gonadectomy.
§§ Depends on method of quantifying analgesia.
||| Greater analgesia in females after gonadectomy.
### Effect was dose-dependent.
*** Significant differences were found when comparing O VX with ET-treated females.
††† Morphine sensitivity restored after TP, but not ET, in females.
†††§ Morphine sensitivity varied over estrous cycle, but specific phases not reported.
§§§ Clear trend toward decreased analgesia.

Sex Hormones and Opioid Analgesia. Given the ubiquitous actions and sex differences of sex steroids in the CNS, it is not surprising that many investigators have attempted to relate sex differences in opioid analgesia to gonadal hormone levels (table 2). Indeed, estrous phase modulates the expression of morphine analgesia. Whereas intact rats are more sensitive to the analgesic effects of morphine on the mornings of diestrus85 and proestrus85,86 after systemic administration, the magni-
tude of morphine analgesia is larger during proestrous and estrous after its administration directly into the CNS.

However, in mice, opioid sensitivity does not vary throughout the estrous cycle. Studies with ovariectomized subjects are less consistent. Whereas systemic morphine analgesia is increased in ovariectomized females relative to sham-operated controls on the hot-plate test, no significant effect is observed in a visceral nociceptive assay. Because ovariectomy also increased supraspinal morphine analgesic sensitivity against electric shock and thermal nociception (i.e., tail-flick test), it might be argued that gonadal hormones have different effects on different nociceptive modalities. However, although adult ovariectomy has been reported to reduce the magnitude but not potency of morphine analgesia on the tail-flick test in rats after central and systemic administration, morphine analgesia after systemic administration has also been reported to be increased or not changed. Therefore, conflicting results are also observed using the same nociceptive assay. Exposure to estradiol or progesterone replacement therapy in ovariectomized rats decreased morphine analgesia on the hot-plate test, although the effect of the lower progesterone dose varied with time of treatment. In intact rats, however, simulating pregnancy concentrations of estradiol 17-β and progesterone in nonpregnant rats increased responsiveness to the k-OR agonist U-50,488H after spinal administration. The effect of gonadectomy on morphine analgesia in male rats and mice are similarly inconsistent. There are reports of both reduced and unaltered systemic morphine analgesia for rats on the tail-flick test after castration. Again, the effects of castration may be nociceptive modality-specific because increased morphine analgesia on the hot-plate test is also observed. Similar to results in female rats, ICV morphine injections in castrated male rats produces analgesia on the tail-flick and jump tests that is reduced in efficacy but not potency. This effect may be CNS region-dependent because morphine potency after microinjection into the ventrolateral periaqueductal gray in castrated male rats is slightly increased. Generalizations can not be made from morphine to other µ-OR agonists because gonadectomy failed to consistently affect analgesia produced by ICV injections of DAMGO. Gonadectomy was similarly without effect on the δ-OR analgesia of DSLET.

In male mice, morphine analgesia after castration is increased on the hot-plate test and against abdominal writhing induced by acetic acid but decreased on the tail-flick test. Testosterone reversed the attenuated morphine sensitivity of the castrated rat. In fact, whereas estradiol 17-β and progesterone had no significant effect on morphine potency in intact male rats, testosterone produced biphasic effects, first potentiating (30 min) then attenuating (4 h) systemic morphine analgesia. Testosterone, but not estradiol 17-β or progesterone alone or in combination, also restored morphine potency in ovariectomized and postpartum rats, in which normal ovarian activity is halted. These findings suggest that testosterone regulates morphine sensitivity in female rats. However, the progesterone metabolite 17α-hydroxyprogesterone had no effect on morphine analgesia per se but antagonized the effect of testosterone in restoring morphine sensitivity in ovariectomized rats, suggesting an interaction between ovarian steroids in modulating morphine potency. Ovariectomy also eliminates the age-related attenuation (see µ-Opioid Receptor Agonists) in the potency and magnitude of morphine analgesia relative to intact females, but castration had only marginal effects on the increased morphine analgesia observed in aged males. Finally, the role of gonadal hormones in the adaptive changes after chronic morphine may differ between the sexes because ovariectomized rats developed somewhat less morphine tolerance than estradiol-treated females, but castration and testosterone supplementation does not affect morphine tolerance in males.

It should be noted, however, that sex steroids exert widespread short- and long-term effects on cellular physiology and organization, and there is significant variability among studies with regard to the age of the animals at the time of, and the latencies between, ovariectomy, hormone replacement therapy, and nociceptive testing (table 2). This lack of uniform methodology may contribute to the apparent confusion in the literature.

**Mechanisms of Sex Hormone Action on Opioid Analgesia.** Apparent inconsistencies notwithstanding, the mechanism by which gonadal hormonal milieu may modulate opioid analgesia remains unknown. For example, there are conflicting reports regarding the effect of castration on ORs. Whereas increased OR density has been reported for rats, other investigators report no changes in OR density or affinity in rats and mice. In female rats, ovarian steroid treatment and ovariectomy alters brain opioid binding sites. This regulation may occur at the level of the gene as progesterone increases levels of µ-OR mRNA in hypothalamic regions of ovariectomized, estradiol-treated rats. However, as noted previously, it is unlikely that sex differences in OR binding in intact mice or rats is a viable explanation for
sex differences in analgesia. Kepler et al. suggest that the colocalization of opioid and gonadal steroid receptors in the mesencephalic central gray and amygdala may allow gonadal hormones to modulate opioid analgesia. They also suggest that gonadal hormones interact with transmitters relevant to opioid analgesia (e.g., serotonin and the opioid peptides leu- and met-enkephalin), whose concentrations differ in males and females in these regions. Indeed, estradiol has been shown to control opioid peptide synthesis in the hypothalamus at rates that differ between the sexes and throughout the estrous cycle in females, and ovariectomy alters levels of the opioid peptides leu- and met-enkephalin and dynorphin A and B. In this context, Krzanowska and Bodnar suggested that their observation of sex differences in morphine analgesia after microinjections into the ventrolateral periaqueductal gray may result from this region’s interaction with estradiol-containing hypothalamic nuclei, and ultimately, its opioid peptide content. The relevance of these interactions in the analgesic effects of morphine and other opioids, however, has not been shown.

**Human Studies**

In humans, sex differences in opioid analgesia have been studied minimally and remain poorly understood. In early studies in which patient sex was considered, such comparisons were not the primary focus of investigation, resulting in inadequate controls for confounding variables such as weight, age, and placebo effect. For example, in one study, female cancer patients required smaller doses of orally administered diamorphine and morphine than male cancer patients, but patient weight was not considered, and more women also received an anxiolytic. Recent better-controlled studies continue to suggest that opioids may be more effective analgesics in women compared with men, but the presence or absence of sex differences in humans may depend on variables similar to those affecting animal studies, such as the pharmacologic profile of the opioid used. For example, whereas females report greater pain relief from the μ-OR agonists pentazocine, nalbuphine, and butorphanol after dental (molar extraction) surgery, no sex differences were reported in the efficacy of morphine for the same procedure. However, sex differences in opioid use and efficacy in clinical pain may reflect differences between men and women in reporting pain and seeking pain relief and by unwarranted psychogenic attributions made by health care providers regarding pain in women. For example, in one study, physicians were evaluated for their attitudes toward two hypothetical patients presenting with either headache or abdominal pain. By changing only the gender of nouns and pronouns, two otherwise identical versions were constructed. Female patients were deemed to be as ill as male patients, but were also judged to be more emotional. It has been suggested that this tendency of primary care physicians to regard women as more emotionally labile and more apt exaggerate complaints of pain than men contributed to the tendency to prescribe sedatives to women but morphine to men recovering from coronary artery bypass graft. This problem may be partly circumvented in studies in which opioid analgesia is managed by the patient. Miaskowski and Levine reviewed studies from 1966 to 1998 in which a patient-controlled analgesia apparatus was used to administer opioids with a predominantly μ-OR site of action for postoperative pain in men and women. A slight majority of the studies noted larger patient-controlled opioid consumption in males. The authors offered several possible explanations for gender differences in opioid consumption, in addition to their hypothesis that opioids may be more effective analgesics in women. These include sex differences in fear of addiction, previous pain experience, and tolerance to postoperative pain and opioid side-effects. Importantly, it has been noted that these studies did not evaluate opioid analgesia, only consumption, and it is unknown whether increased consumption in males belies a decreased analgesic effect in this sex.

**Conclusions**

The available animal and human data indicate that sex may affect opioid analgesia but that the direction and magnitude of these differences depend on many interacting variables. These include those specific to the drug itself, such as the dose, pharmacology, and route and time of administration, and those particular to the subject, such as species, type of pain, genetic background, age, and gonadal–hormonal status. When considering sex differences in the analgesic effects of opioids, we should also consider the vast literature documenting sex differences in pain perception per se, which has been recently reviewed. It is beyond the scope of the current review to comment on the possible contribution of sex differences in pain perception on the ability of opioids to differentially inhibit pain in males and females. However, given the multitude of CNS substrates and...
systems underlying both pain and opioid analgesia and the possibility that only some differ between sexes, we could reasonably expect to encounter sex differences in opioid analgesic efficacy in some instances but not others, depending ultimately on the nature of the pain stimulus and opioid involved, as outlined previously.

Despite evidence of sex related differences, variability in patient opioid analgesic sensitivity should compel practitioners to customize their dosing regimens based on individual requirements. The studies presently reviewed suggest that patient gender may contribute to this variability. We also note that sex differences in analgesia are not limited to opioid drugs. Differences in analgesic sensitivity between males and females is observed after administration of diverse classes of nonopioid compounds such as nicotine, cocaine, and cholinergic and noradrenergic agonists.64,65 Furthermore, activation of endogenous pain inhibitory mechanisms in response to stress also produces magnitudes of analgesia that differ between the sexes, regardless of whether analgesia is mediated by endogenous opioid peptides.66 Therefore, sex differences in analgesia arise from seemingly fundamental and ubiquitous differences in endogenous pain inhibitory circuitry. Further studies are needed to clarify the conditions in which patient gender considerations will afford the most efficacious use of opioids for the control of pain.

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