

## REVIEW ARTICLE

# Consensus statements on the clinical understanding and use of milnacipran in Hong Kong

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## Abstract

**Objective:** Our aim is to develop a local consensus to guide medical practitioners and psychiatrists on the use of milnacipran in different psychiatric conditions.

**Methods:** By utilizing the modified Delphi technique, 12 statements were electronically voted on anonymously for their practicability of recommendation.

**Results:** There was a very high degree of agreement among the consensus group on 10 finalized consensus statements, but 2 statements were voted down due to a poor degree of agreement.

**Conclusions:** The present consensus statements were developed as general recommendations for medical practitioners and psychiatrists to be practically referred to in clinical settings.

## KEYWORDS

consensus statements, Hong Kong, milnacipran

## 1 | OBJECTIVES

Milnacipran hydrochloride is a serotonin and norepinephrine reuptake inhibitor (SNRI), with a balanced potency for the inhibition of serotonin and noradrenaline reuptake (Boyer & Briley, 1998; Forest Laboratories Inc., 2009; Papakostas & Fava, 2007). In view of the variations in drug response due to genetic differences and the lack of local evidence-based treatment guidelines, a consensus meeting was organized to

develop a local consensus to guide medical practitioners and psychiatrists on the use of milnacipran in different psychiatric conditions.

## 2 | METHODS

A consensus meeting was held in Hong Kong, with the consensus group composed of local clinical health-care professionals experienced

in the management of major depressive disorder. The literature search was performed using the PUBMED database with the following keywords: "milnacipran," "major depressive disorder," and "side effects." Following this review, 28 of 117 references were included for discussion by the consensus group.

The consensus group utilized the modified Delphi technique (Linstone & Turoff, 2002; Ooi et al., 2010) to facilitate a formal face-to-face expert focus meeting. After a comprehensive review and discussion, 12 statements on milnacipran were finalized and voted on anonymously using electronic voting devices. Each statement was rated according to both (a) quality of evidence and (b) practicability of recommendation in Hong Kong. A consensus statement was only accepted if at least 80% voted "A" or "B" for practicability (Table 1).

### 3 | RESULTS

After tabulating the voting results on the 12 statements, 10 were ultimately accepted by the consensus group, with two statements voted down due to a poor degree of agreement (Table 2). Details of each statement are discussed in the following section.

### 4 | DISCUSSION

**Statement 1.** *Milnacipran acts primarily as a selective serotonin and norepinephrine reuptake inhibitor (SNRI), which is registered in Hong Kong for the treatment of major depressive disorder.*

Quality of evidence: I

Practicability of recommendation: A—91.66%, B—8.34%, C—0%, D—0%, E—0%.

In Hong Kong, milnacipran is indicated for the treatment of major depressive episodes in adults. The efficacy of milnacipran has been demonstrated in several clinical studies, and it has also been shown to be as efficacious as other antidepressants, including fluvoxamine and paroxetine, for the treatment of major depressive disorder (Papakostas & Fava, 2007).

**Statement 2.** *Milnacipran can be considered in patients experiencing side effects from other antidepressants with affinity to postsynaptic adrenergic, muscarinic and*

*histaminic receptors.*

Quality of evidence: I

Practicability of recommendation: A—58.33%, B—33.33%, C—8.34%, D—0%, E—0%.

Alpha<sub>1</sub>-adrenoceptors, muscarinic, or histaminergic H<sub>1</sub> receptors are thought to be responsive for the orthostatic hypotension, anticholinergic effects (dry mouth, constipation, and blurred vision), and sedation seen with tricyclic antidepressants (TCAs; Poirier et al., 2004). Unlike most TCAs, milnacipran has no affinity for α<sub>1</sub>-adrenergic or histamine H<sub>1</sub> receptors (Boyer & Briley, 1998; Puozzo, Panconi, & Deprez, 2002). Results from clinical trials have shown that milnacipran at single doses of up to 100 mg does not exert disruptive effects on cognitive function and psychomotor performance (Hindmarch, Rigney, Stanley, & Briley, 2000; Puozzo et al., 2002).

**Statement 3.** *Milnacipran can be considered as the drug of choice for patients aged 50 years or older, because it is devoid of cognitive side effects.*

Quality of evidence: I

Practicability of recommendation: A—16.67%, B—8.34%, C—16.67%, D—41.65%, E—16.67%.

This statement was derived primarily from a double-blind trial comparing the efficacy and safety of milnacipran (50 mg twice daily) with that of imipramine (50 mg twice daily) among elderly patients with major depressive disorder (Tignol et al., 1998). The study results showed that milnacipran may be superior to imipramine in elderly depressed patients due to the significantly fewer side effects observed, especially anticholinergic effects, and the same antidepressant activity as imipramine (Tignol et al., 1998). Additionally, milnacipran does not cause cognitive impairment (Hindmarch et al., 2000; Poirier et al., 2004; Tignol et al., 1998).

Despite the above-mentioned study findings, current evidence was deemed inadequate to support the statement, and it was voted down by the panel due to a poor degree of agreement.

**Statement 4.** *Milnacipran is the drug-of-choice for patients with specific needs, including those with hepatic impairment and polypharmacy, because it is characterized by low protein binding, predominant renal clear-*

**TABLE 1** The grading system for each consensus statement during the voting session

Quality of evidence	Classification of recommendation	Practicability of recommendation
I: Evidence obtained from at least 1 randomized controlled trial	A: There is good evidence to support the statement	A: Accept completely
II-1: Evidence obtained from well-designed control trials without randomization	B: There is fair evidence to support the statement	B: Accept with some reservation
II-2: Evidence obtained from well-designed cohort or case-control study	C: There is poor evidence to support the statement, but recommendation made on other grounds	C: Accept with major reservation
II-3: Evidence obtained from comparison between time or places, with or without intervention	D: There is fair evidence to refute the statement	D: Reject with reservation
III: Opinion of respected authorities, based on clinical experience and expert committee	E: There is good evidence to refute the statement	E: Reject completely

Note. Modified from the Canadian Task Force on the Periodic Health Examination (Ooi et al., 2010).

**TABLE 2** Accepted and rejected consensus statements as decided by panel voting

Number	Finalized consensus statements	Accepted by the panel (yes/no)
1	Milnacipran acts primarily as a selective serotonin and norepinephrine reuptake inhibitor (SNRI), which is registered in Hong Kong for the treatment of major depressive disorder.	Yes
2	Milnacipran can be considered in patients experiencing side effects from other antidepressants with affinity to postsynaptic adrenergic, muscarinic, and histaminic receptors.	Yes
3	Milnacipran can be considered as the drug of choice for patients aged 50 years or older, because it is devoid of cognitive side effects.	No
4	Milnacipran is the drug of choice for patients with specific needs, including those with hepatic impairment and polypharmacy because it is characterized by low protein binding, predominant renal clearance, and limited CYP450 liver metabolism (thus low potential for drug–drug interactions).	Yes
5	Milnacipran normally does not require slow dosage titration.	No
6	Milnacipran should be prescribed with caution in patients with specific medical conditions, such as hypertension, compromised kidney functions, cardiac disease, seizures or history of seizures, closed-angle glaucoma, and syndrome of inappropriate antidiuretic hormone secretion. Dosage should be adjusted in patients with severe renal impairment.	Yes
7	Caution should be exercised when milnacipran is administered to a breastfeeding woman; it can be excreted into human milk. The effects of milnacipran in the nursing infant are unknown.	Yes
8	Milnacipran may affect urethral resistance and micturition. Dysuria occurred more frequently in patients treated with milnacipran than in placebo-treated patients (1% vs. 0.5%). Caution must be exercised when milnacipran is administered in patients with lower urinary tract symptoms, particularly those with benign prostatic hyperplasia or prostatitis.	Yes
9	Milnacipran is generally well tolerated. Nausea (35%) is the most frequent side effect of milnacipran. Other side effects include dysuria (2%), constipation (16%), hot flush (11%), hyperhidrosis (8%), palpitations (8%), dry mouth (5%), increased blood pressure (7%, with mean increases of up to 3.1 mmHg in systolic blood pressure and diastolic blood pressure), headache (19%), dizziness (11%), and insomnia (12%).	Yes
10	Clinicians should be aware of rare but serious side effects of milnacipran, including angina pectoris, supraventricular extrasystoles, ventricular extrasystoles, convulsion, encephalopathy, deep vein thrombosis, and severe hyponatremia.	Yes
11	Milnacipran, with a balanced inhibition of serotonin and noradrenaline reuptake, appears to be less associated with sexual dysfunction, which is thought to arise largely through stimulation of 5-HT <sub>2A</sub> receptors.	Yes
12	When compared with tricyclic antidepressants, milnacipran exerts little effect on the cardiovascular system and it is less lethal in case of overdose.	Yes

**ance, and limited CYP450 liver metabolism (thus low potential for drug–drug interactions).**

Quality of evidence: I

Practicability of recommendation: A–83.33%, B–16.67%,

C–0%, D–0%, E–0%.

At a therapeutic dose, plasma protein binding of milnacipran is low (13%) and non-saturable (Boyer & Briley, 1998; Lambert & Bourin, 2002; Puozzo et al., 2002). Metabolism of milnacipran is not via CYP enzymes, which limits the risk of drug interactions, particularly in older subjects taking many medicines (Lambert & Bourin, 2002; Puozzo et al., 1998; Puozzo et al., 2002). Unchanged drug exposure is not modified in liver-impaired subjects, whereas plasma levels of the conjugate are slightly decreased compared with the control group. As the unchanged drug is the only compound responsible for the activity of milnacipran, no dosage adjustment is needed in patients presenting with liver impairment (Puozzo et al., 1998).

**Statement 5. Milnacipran normally does not require slow dosage titration.**

Quality of evidence: III

Practicability of recommendation: A–8.33%, B–16.67%,

C–25%, D–25%, E–25%.

This statement was formulated on the basis of a literature review, which suggested that dosage titration is not required for milnacipran

(Spencer & Wilde, 1998). However, recent clinical data and real-life practice did not support the statement, and it was rejected by the panel.

**Statement 6. Milnacipran should be prescribed with caution in patients with specific medical conditions, such as hypertension, compromised kidney functions, cardiac disease, seizures or history of seizures, closed-angle glaucoma, and syndrome of inappropriate antidiuretic hormone secretion. Dosage should be adjusted in patients with severe renal impairment.**

Quality of evidence: I (II-3 for syndrome of inappropriate antidiuretic hormone secretion)

Practicability of recommendation: A–100%, B–0%, C–0%, D–0%, E–0%.

The SNRIs, including milnacipran, have been associated with increases in heart rate and blood pressure (Higuchi & Briley, 2007; Hussar, 2009; Trugman, Palmer, & Ma, 2014; Vitton, Gendreau, Gendreau, Kranzler, & Rao, 2004). Preexisting hypertension or other cardiovascular disease should be treated before starting therapy with milnacipran (Hussar, 2009). Blood pressure and heart rate monitoring is recommended at treatment initiation, following dosage increases and periodically throughout the treatment with milnacipran for all patients and more closely in patients with known cardiovascular risk (Hussar, 2009). Cases of seizures have been reported in subjects receiving milnacipran during clinical trials (Leinonen, Lepola, Koponen,

Mehtonen, & Rimon, 1997). Mydriasis may occur in patients treated with an SNRI, including milnacipran (Hussar, 2009). The use of the new drug is contraindicated in patients with uncontrolled narrow-angle glaucoma and must be used with caution in those with controlled narrow-angle glaucoma (Hussar, 2009). Cases of hyponatremia, probably due to a syndrome of inappropriate antidiuretic hormone secretion, have been observed in patients receiving medicinal products that inhibit serotonin reuptake (Harsha, Manimekalai, Sivaprakash, Jagan, & Pooja, 2015; Hussar, 2009).

**Statement 7. Caution should be exercised when milnacipran is administered to a breastfeeding woman; it can be excreted into human milk. The effects of milnacipran in the nursing infant are unknown.**

Quality of evidence: III

Practicability of recommendation: A—91.66%, B—8.34%, C—0%, D—0%, E—0%.

Milnacipran is classified as a pregnancy risk Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus (Hussar, 2009). Whether or not the new drug is excreted in human milk is unknown, and nursing while being treated with the drug is not recommended (Hussar, 2009).

**Statement 8. Milnacipran may affect urethral resistance and micturition. Dysuria occurred more frequently in patients treated with milnacipran than in placebo-treated patients (1% vs. 0.5%). Caution must be exercised when milnacipran is administered in patients with lower urinary tract symptoms, particularly those with benign prostatic hyperplasia or prostatitis.**

Quality of evidence: I

Practicability of recommendation: A—91.66%, B—8.34%, C—0%, D—0%, E—0%.

Because of the noradrenergic effect, milnacipran may affect urethral resistance and micturition (Hussar, 2009). Male patients are more prone to genitourinary adverse effects, such as dysuria or urinary retention, and may experience testicular pain or ejaculation disorders (Forest Laboratories Inc., 2009).

**Statement 9. Milnacipran is generally well tolerated. Nausea (35%) is the most frequent side effect of milnacipran. Other side effects include dysuria (2%), constipation (16%), hot flush (11%), hyperhidrosis (8%), palpitations (8%), dry mouth (5%), increased blood pressure (7%, with mean increases of up to 3.1 mmHg in systolic blood pressure and diastolic blood pressure), headache (19%), dizziness (11%), and insomnia (12%).**

Quality of evidence: I

Practicability of recommendation: A—91.66%, B—8.34%, C—0%, D—0%, E—0%.

Only dysuria occurs more frequently with milnacipran compared with TCAs or selective serotonin reuptake inhibitors (Lambert & Bourin, 2002). Nausea occurs less frequently with milnacipran when compared with selective serotonin reuptake inhibitors (Lambert & Bourin, 2002). Compared with TCAs, dry mouth, constipation, tremor,

sweating, somnolence, tiredness, and giddiness occur less frequently in milnacipran-treated patients (Lambert & Bourin, 2002).

**Statement 10. Clinicians should be aware of rare but serious side effects of milnacipran, including angina pectoris, supraventricular extrasystoles, ventricular extrasystoles, convulsion, encephalopathy, deep vein thrombosis, and severe hyponatremia.**

Quality of evidence: I

Practicability of recommendation: A—83.33%, B—16.67%, C—0%, D—0%, E—0%.

Milnacipran has been reported to be a potential cause of hyponatremia (Matsumoto, 2005). Serum sodium concentrations should be monitored not only in the first few weeks of therapy but also during the entire course for early detection and treatment of hyponatremia (Matsumoto, 2005). Rare but serious side effects such as angina pectoris, supraventricular extrasystoles, ventricular extrasystoles, convulsion, encephalopathy, and deep vein thrombosis were reported in a 48-week open-label extension study of 825 patients receiving flexible-dose (40–120 mg/day) levomilnacipran extended release (Mago, Forero, Greenberg, Gommoll, & Chen, 2013).

**Statement 11. Milnacipran, with a balanced inhibition of serotonin and noradrenaline reuptake, appears to be less associated with sexual dysfunction, which is thought to arise largely through stimulation of 5-HT<sub>2A</sub> receptors.**

Quality of evidence: I

Practicability of recommendation: A—66.67%, B—33.33%, C—0%, D—0%, E—0%.

Milnacipran appears to improve sexual function in parallel with improvement in other symptoms of depression (Baldwin, Moreno, & Briley, 2008). From a 12-week open study and a 6-week randomized controlled study, all sexual function and enjoyment questionnaire items showed improvements in sexual function in both studies at end-point, with 60% (12 weeks) and 56% (6 weeks) of patients stating that their sexual desire was as great as or greater than it had been before their depressive episode (Baldwin et al., 2008).

**Statement 12. When compared with tricyclic antidepressants, milnacipran exerts little effect on the cardiovascular system and it is less lethal in case of overdose.**

Quality of evidence: I

Practicability of recommendation: A—50%, B—50%, C—0%, D—0%, E—0%.

Milnacipran does not induce any significant clinical change in cardiac repolarization or conduction (Lambert & Bourin, 2002). According to a review of seven clinical trials comparing milnacipran 50 mg twice daily and TCAs 75 mg twice daily, because milnacipran exerts fewer cardiovascular effects than TCAs, it is widely expected to be much safer in overdose (Kasper, Pletan, Solles, & Tournoux, 1996). Fifteen cases of intentional overdose of milnacipran were reported during clinical trials, with ingested quantities of up to 2,800 mg taken either alone or in association with other therapeutic agents. There have been no deaths, and the outcome of these incidences was favorable in all cases (Boyer & Briley, 1998). Since commercialization in France, quantities of

up to 5,600 mg milnacipran (2-month supply) have been taken in intentional or accidental overdose with no serious consequences (Boyer & Briley, 1998).

## 5 | CONCLUSIONS

The consensus group reached a unanimous agreement on 10 statements regarding the use of milnacipran in Hong Kong. The present consensus statements were developed as general recommendations for medical practitioners and psychiatrists to be practically referred to in clinical settings.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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## Consensus Statements on the Clinical Understanding and Use of Bupropion in Hong Kong

Number	Finalised consensus statements
1	Besides treatment for major depressive disorder, bupropion is also indicated for seasonal affective disorder and is particularly useful for patients with anhedonia, reduced motivation, weight concern, and sexual dysfunction.
2	Off-label use of bupropion includes smoking cessation, attention deficit hyperactivity disorder (ADHD), bipolar depression, depression in Parkinson's disease, and occasionally some anxiety disorders.
3	Bupropion is a unicyclic anti-depressant with dual action on dopamine and noradrenaline, but has no effect on serotonin.
4	Bupropion is an effective anti-depressant as monotherapy, but is also an adjuvant medication in cases of incomplete response to SSRI anti-depressants.
5	Bupropion is generally well tolerated; the most common side effects include dry mouth, headache and insomnia; it should be avoided at bedtime.
6	Bupropion should be used with caution in patients with hypertension or cardiovascular comorbidities. It is not recommended in patients at risk of seizures, eating disorders, psychosis, and closed-angle glaucoma.
7	Bupropion should not be used in patients receiving monoamine oxidase inhibitors, and its combination with venlafaxine may lead to a dose-dependent increase in blood pressure.
8	Smoking and alcohol use do not appear to interact with bupropion, but its serum concentration may be increased by zinc supplementation.
9	Bupropion overdose rarely results in death but may lead to seizures, hallucinations, delusions, vomiting, and aggressive behaviour.
10	Abrupt withdrawal of bupropion can result in discontinuation syndrome, which may manifest as dystonia, irritability, anxiety, mania, headache, aches and pains.
11	Use of bupropion during pregnancy may lead to foetal cardiac malformation during the first trimester.

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