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VIEWPOINT

Trazodone generates m-CPP: In 2008 risks from m-CPP might outweigh benefits of trazodone

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Abstract
Since deleterious effects of *m*-CPP, the primary catabolic metabolite of trazodone, were last reviewed 2 years ago, research data continue to accrue showing that clinically significant levels of *m*-CPP (a) are generated in patients using trazodone for sleep and (b) are present 24 h a day and (c) have potentially serious ill effects. This commentary argues that the documented potential for harm and multiple risks of *m*-CPP outweigh potential benefits of trazodone, given the development and marketing of many safer alternatives since trazodone's introduction in the 1980s.

Key words: *Anxiety, fibrosis, inflammation,* m-*CPP, trazodone*

Introduction

In 2008 trazodone is still commonly recommended as an antidepressant (Quaseem et al. 2008) and sleep aid (Flannagan et al. 2007; Roth 2008). Its current clinical use is mainly as sleep aid. This commentary reviews recent data leading to a conclusion that continued trazodone use should be re-considered and curtailed. Trazodone's primary metabolic catabolite is *m*-clorophenylpiperazine, *m*-CPP. A previous review (Kast 2007) concluded that *m*-CPP risks might not be worth the benefits of trazodone, this update now concludes the same. Wider awareness of the large database that continues to accrue, showing potential harm of *m*-CPP, is important.

Known by various trade names (Desyrel, Molipaxin, Trittico, Thombran and Trialodine) trazodone is cheap, available generically, and relatively safe in single-drug overdose. The central problem of trazodone is its hepatic catabolism by CYP3A4 to *m*-CPP, as shown in Figure 1. Basic pharmacological and pharmacokinetic properties of *m*-CPP are listed in Table I.

m-CPP is generated also from the trazodone-related antidepressant nefazodone (Barbhaiya et al. 1996). Nefazodone was withdrawn from the market in most countries in 1996 due to hepatotoxicity.

Initial, middle, or late insomnia are core features of depression. The selective serotonin reuptake inhibitors, SSRIs, though comprising the mainstay of current treatment of depression can fragment sleep further even when they are effective in alleviating the mood disorder (Pandi-Perumal et al. 2008). In current clinical practice, trazodone, as a sleep-enhancing antidepressant, is often added to counter or correct SSRI induced sleep fragmentation.

High and clinically significant daytime *m*-CPP levels (about 100 ng/ml or a tenth of plasma trazodone levels) continue to be documented during in normal humans taking a common trazodone dose for sleep, 150 mg once at bedtime (Mercolini et al. 2008). This is comparable to levels attained when anxiety or panic attacks are provoked by i.v. *m*-CPP in studies with normal human volunteers (Van Veen et al. 2007).

An odd street drug-of-abuse

m-CPP is becoming a street drug-of-abuse. Some patients report pleasant or desirable feelings after

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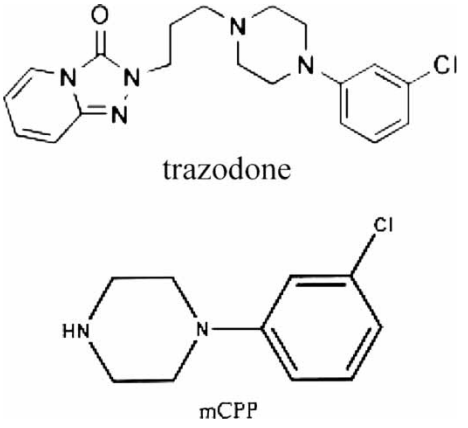

Figure 1. Chemical structures of trazodone and *m*-CPP.

ingesting street *m*-CPP but most people report headaches, anxiety, panic, confusion, and depressed mood (Kovaleva et al. 2008). Patients presenting with acute *m*-CPP ingestion often report dysphoria and show great distress without being able to further specify or add detail. A similar clinical picture is often obtained after research administration of *m*-CPP to young healthy human volunteers (Gijsman et al. 1998; Feuchtl et al. 2004).

Street *m*-CPP tablets, sold as "LSD", "ecstasy", "dumpers", "rainbows", and other names, are usually characteristically multicolored tablets containing 20–40 mg *m*-CPP with unknown contaminants and excipients. A common patient dose is several of these. Expected *m*-CPP blood levels from street ingestion is unknown. Research volunteers with prior experience of the real street drug ecstasy (3,4-methylenedioxymethamphetamine, MDMA) report that *m*-CPP in doses from 17.5 to 52.5 mg/70 kg produced MDMA-like stimulant and hallucinogenic effect (Johanson et al. 2006). *m*-CPP is appearing as an adulterant in cocaine and other street drugs-of-abuse (Staack et al. 2007; Kovaleva et al. 2008).

m-CPP stimulates 5-HT2B and 5-HT2C receptors

m-CPP as potent and clinically relevant agonist at 5-HT2B and 5-HT2C receptors was reviewed previously (Kast 2007). Agonism at 5-HT2B or 5-HT2C is expected to be destructive psychiatrically and somatically. Additional observations since 2006 confirm and extend that data:

(a) *m*-CPP agonism at 5-HT2B and 5-HT2C receptors was shown to be either anxiolytic or anxiogenic, depending on specific brain location of *m*-CPP infusion in mice (Nunes-de-Souza et al. 2008).

(b) It is the 5-HT2B agonism by pergolide in humans treated for parkinsonism that generates and is the direct cause of tricuspid and mitral valve fibrosis in a fifth of those so treated (Junghanns et al. 2007; Görnemann et al. 2008). Several hundred percent increased risk of clinically significant cardiac valve fibrosis after pergolide was seen (Schade et al. 2007), leading to pergolide's withdrawal from the US market. It is not unreasonable to suspect similar pro-fibrosis *m*-CPP mediated consequences of trazodone use.

(c) 5-HT2B receptor density on pulmonary artery endothelium is increased in pulmonary hypertension. Stimulation of 5-HT2B receptors is crucial for the associated pulmonary artery fibrosis (Launay et al. 2002). A long history associates fibrosis of liver, lung, cardiac valves, and retroperitoneal space with 5-HT2B agonism (Ruddell et al. 2006; Kast et al. 2007).

(d) 5-HT2C agonists stimulate neurons in the suprachiasmatic nucleus, generating a light-mimetic effect, further disrupting day-night cycles (Varcoe et al. 2008).

Table I. Some basic pharmacology and pharmacokinetics of *m*-CPP. "Tobacco" is underlined as a strong CYP 3A4 inducer only because of its ubiquity.

$T_{1/2}$	3–6 h
T_{max}	Wide inter-individual variation (h)
C_{max}	Unknown
Generated by	Hepatic metabolism of trazodone or nefazodone by CYP3A4
Catabolism	By CYP 2D6 to inactive hydroxy-*m*-CPP (renal excretion)
Some common, strong, hepatic CYP3A4 inhibitors	Indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin
Some common hepatic CYP3A4 inducers	Efvirenz, nevirapine, barbituates, carbamazapine, modafinil, pioglitazone, troglitazone, tobacco, rifabutin, phenytoin
Average daytime plasma concentration after bedtime dose of 150 mg trazodone	100 ng/ml

m-CPP as anxiogen

m-CPP is a potent anxiogen in humans and rodents, as previously reviewed (Kast 2007). Empirical data supporting the anxiogenic nature of trazodone and *m*-CPP continues to accrue:

(a) A 6-week comparison of trazodone to sertraline found both similarly separated from placebo in lowering depression, but anxiety burden was higher in the trazodone group (Munizza et al. 2006). The occasional patient will have an intolerable anxiety response to trazodone (Munizza et al. 2006).
(b) Concordant rodent studies show anxiogenic properties of *m*-CPP and anxiolytic properties of other experimental selective 5-HT2C antagonists (Bagdy et al. 2001; Harada et al. 2006).
(c) De novo appearance of psychycotic signs and symptoms is rarely noted after trazodone use (Mizoguchi et al. 2005).
(d) Studies into the nature of anxiety and panic continue to use i.v. *m*-CPP to generate signs and symptoms of these disorders in normal human volunteers (Van Veen et al. 2007; Bagady et al. 2002). *m*-CPP levels in these studies (40–100 ng/ml (Van Veen et al. 2007; Bagady et al. 2002)) are comparable to those seen in patients treated for insomnia with trazodone (10 ng/ml *m*-CPP after a single 100 mg trazodone dose in healthy volunteers (Patel et al. 2008), 100 ng/ml in patients treated chronically with 150 mg trazodone at bedtime (Mercolini et al. 2008)). It cannot be excluded that in anxiety generation slope of *m*-CPP concentration change is important as well as actual serum level.

Additional *m*-CPP toxicities

Dose-proportional memory impairment is seen in rats given *m*-CPP (Khaliq et al. 2008). We should worry about similar decrements in humans until formal study can allay such fears.

5-HT2B agonism in a neuroectodermal cell line was shown to result in increased TACE, tumour necrosis factor-alpha converting enzyme (Schneider et al. 2006). TACE is responsible for conversion of outer cell membrane-bound TNF-alpha to soluble, circulating, TNF-alpha. Increased soluble TNF was demonstrated after 5-HT2B agonists (Schneider et al. 2006). If this were to occur in humans, unfortunate pro-inflammatory and fibrogenic consequences can be expected.

Post-mortem study of brain tissue of depressed patients shows evidence of oxidative stress (Michel et al. 2008). We have several lines of evidence that trazodone might increase this brain oxidative stress. Mice exposed to 4 h of stress by watching, hearing, and proximity to cagemates exposed to unpleasant foot electric shocks, similar to depressed patients in the post-mortem study above showed increased brain lipid peroxidation products even though they themselves received no shocks or any noxious stimuli other than proximity to suffering cagemates (Matsumoto et al 1999). Adding *m*-CPP to these stressed mice potentiated increases in lipid peroxidation products (Matsumoto et al 1999). Concordant with these findings are in vitro evidence of oxidative stress from nefazodone and trazodone by mitochondrial potential collapse and glutathione depletion (Dykens et al 2008).

Conclusion

The outlined deleterious effects of trazodone's primary metabolite *m*-CPP probably make trazodone's ongoing use generally inadvisable. Safer alternatives exist for depression and insomnia treatment.

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Statement of interest

None.

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