

Appendix C: Methylene Blue and Serotonin Syndrome

From: [Perioperative Medication Management – Adult/Pediatric – Inpatient/Ambulatory Clinical Practice Guideline](#)

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Summary:

Although the exact mechanism of this drug interaction is unknown, **methylene blue inhibits the action of monoamine oxidase A** - an enzyme responsible for breaking down serotonin in the brain. It is believed that when methylene blue is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity. See Table 1. Psychiatric medications with serotonergic activity.

- **In emergency situations** requiring life-threatening or urgent treatment with methylene blue (as described above), the availability of alternative interventions should be considered and the benefit of methylene blue treatment should be weighed against the risk of serotonin toxicity. If methylene blue must be administered to a patient receiving a serotonergic drug, the serotonergic drug must be immediately stopped, and the patient should be closely monitored for emergent symptoms of CNS toxicity for two weeks (five weeks if fluoxetine [Prozac] was taken), or until 24 hours after the last dose of methylene blue, whichever comes first.
- **In non-emergency situations** when non-urgent treatment with methylene blue is contemplated and planned, the serotonergic psychiatric medication should be stopped to allow its activity in the brain to dissipate. Most serotonergic psychiatric drugs should be stopped at least 2 weeks in advance of methylene blue treatment. Fluoxetine (Prozac), which has a longer half-life compared to similar drugs, should be stopped at least 5 weeks in advance
- Possible signs/symptoms of Serotonin Syndrome: mental status changes, muscle twitching, excessive sweating, shivering or shaking, diarrhea, ataxia, fever
- Treatment with the serotonergic psychiatric medication may be resumed 24 hours after the last dose of methylene blue
- Serotonergic psychiatric medications should not be started in a patient receiving methylene blue. Wait until 24 hours after the last dose of methylene blue before starting the antidepressant.

References:

1. FDA Drug Safety Communication. <http://www.fda.gov/Drugs/DrugSafety/ucm263190.htm#Hcp>. Updated 10/20/2011.
2. Bach KK, Lindsay FW, Berg LS, Howard RS. Prolonged postoperative disorientation after methylene blue infusion during parathyroidectomy. *Anesth Analg*. 2004;99:1573-4.
3. Kartha SS, Chacko CE, Bumpous JM, Fleming M, Lentsch EJ, Flynn MB. Toxic metabolic encephalopathy after parathyroidectomy with methylene blue localization. *Otolaryngol Head Neck Surg*. 2006;135:765-8.

Table 1. Psychiatric medications with serotonergic activity

Generic name	Found in Brand name(s)
Selective Serotonin Reuptake Inhibitors (SSRIs)	
paroxetine	Paxil, Paxil CR, Pexeva
fluvoxamine	Luvox, Luvox CR
fluoxetine	Prozac, Sarafem, Symbyax
sertraline	Zoloft
citalopram	Celexa
escitalopram	Lexapro
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	
venlafaxine	Effexor, Effexor XR
desvenlafaxine	Pristiq
duloxetine	Cymbalta
Tricyclic Antidepressants (TCAs)	
amitriptyline	Amitid, Amitril, Elavil, Endep, Etrafon, Limbitrol, Triavil
desipramine	Norpramin, Pertofrane
clomipramine	Anafranil
imipramine	Tofranil, Tofranil PM, Janimine, Prammine, Presamine
nortriptyline	Pamelor, Aventyl hydrochloride
protriptyline	Vivactil
doxepin	Sinequan, Zonalon, Silenor
trimipramine	Surmontil
Monoamine Oxidase Inhibitors (MAOIs)	
isocarboxazid	Marplan
phenelzine	Nardil
selegiline	Emsam, Eldepryl, Zelapar
tranylcypromine	Parnate
Other Psychiatric Medications	
amoxapine	Asendin
maprotiline	Ludiomil
nefazodone	Serzone
trazodone	Desyrel, Oleptro, Trialodine
bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban, Aplenzin
buspirone	Buspar
vilazodone	Viibryd
mirtazapine	Remeron, Remeron Soltab