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Effects of opioids at monoamine transporters: a potential for interactions of pain medications with antidepressants

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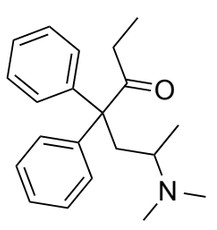
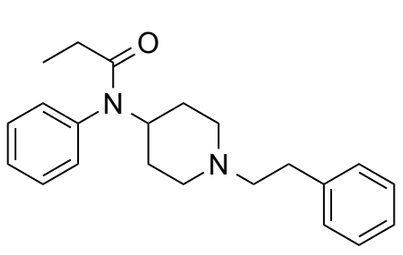
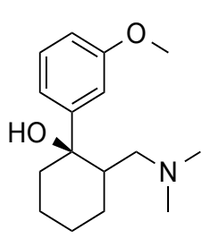
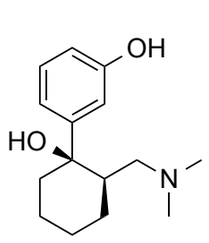
Introduction

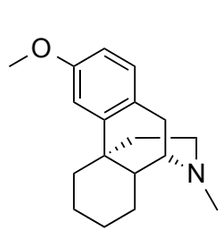
Opioid analgesics primarily act via activation of opioid receptors but some synthetic opioids may also inhibit the reuptake of monoamines. In particular the inhibition of the serotonin reuptake has been described to increase the risk for serotonergic toxicity (serotonin syndrome, fig 2), which may be fatal if untreated. Especially antidepressants inhibiting serotonin reuptake are often consumed together with pain medication, including over the counter cough medication containing dextromethorphan. Therefore this potential interaction needs careful attention.











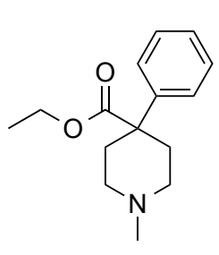


Figure 1: Chemical structures of atypical synthetic opioids

Study aim

The aim of this in vitro study was to assess how potent clinically used synthetic opioids inhibit the reuptake transporters for serotonin (SERT; 5-HT) and norepinephrine (NET; NE), in contrast to pure opioid-receptor agonists like morphine. We included the atypical synthetic opioids tramadol, o-desmethyl-cis-tramadol, dextromethorphan, pethidine, methadone and its enantiomers, and fentanyl in this study.

Methods

We assessed 5-HT and NE reuptake inhibition in human embryonic kidney (HEK) 293 cells, stably expressing the respective human monoamine transporter [1, 2]. The amount of remaining radiolabeled monoamines in the cells was measured and these results were fitted with non-linear regression to sigmoidal dose-response curves. IC50 values with 95% confidence intervals (CI) were calculated using Prism (GraphPad, San Diego, CA, USA).

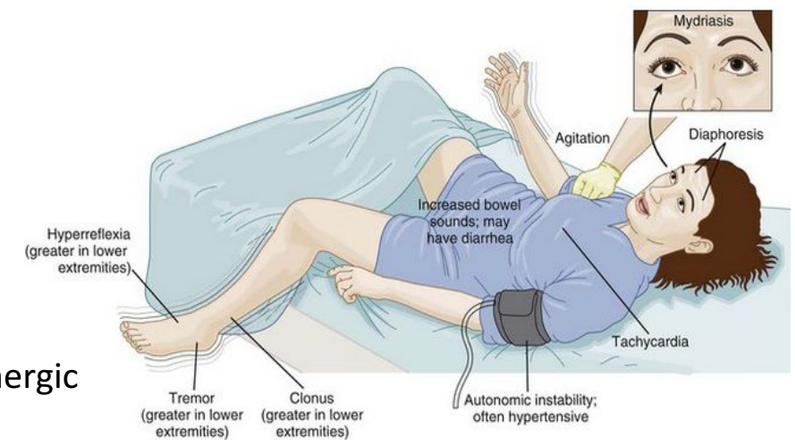
Table 1: Inhibition potencies for SERT and NET

	SERT		NET		
	IC50 [µM]	(95% CI)	IC50 [µM]	(95% CI)	SERT/NET ratio
Dextromethorphan	0.068	(0.047-0.100)	5.77	(3.86-8.63)	84.9
Fluoxetine	0.092	(0.076-0.112)	na	na	na
Methadone	0.27	(0.19-0.39)	7.52	(4.64-12.18)	27.9
d(S)-Methadone	5.61	(3.92-8.02)	68.6	(41.5-113)	12.2
l(R)-Methadone	0.28	(0.21-0.37)	2.61	(1.90-3.56)	9.32
Pethidine (=Meperidine)	1.55	(0.95-2.52)	1.78	(1.13-2.79)	1.15
Tramadol	3.33	(2.72-4.09)	2.07	(1.38-3.10)	0.62
Fentanyl	154	(107-222)	50.0	(37.1-67.4)	0.32
O-Desmethyl-cis-tramadol	24.0	(15.8-36.3)	6.13	(4.62-8.13)	0.26
Venlafaxine	na	na	0.41	(0.30-0.56)	na

Values are means of three to four independent experiments and 95% confidence intervals (CI).
SERT/NET ratio: 1/SERT IC_{50}:1/NET IC_{50}

+

- SSRI's
- Other serotonergic drugs



http://clinicalgate.com/antidepressants-and-antipsychotics/

Figure 2: Clinical manifestation of serotonergic toxicity

Results

- Atypical opioids inhibited the reuptake of 5-HT and NE but with high differences among the compounds.
- Dextromethorphan was the most potent SERT –inhibitor and inhibited SERT with a similar IC50 value as the therapeutically used selective serotonin reuptake inhibitor (SSRI) fluoxetine.
- Racemic methadone was more potent than tramadol and pethidine, with a higher potency for the l(R)-methadone thank d(S)-methadone, found for both transporters.
- O-Desmethyl-cis-tramadol and fentanyl were weak SERT inhibitors and relatively more potent at NET.
- Most atypical opioids also inhibited NET: Tramadol and pethidine showed dual SERT and NET inhibition whereas dextromethorphan and methadone were SERT selective inhibitors.

Conclusion

The presented data indicate a dual mechanism for a large group of synthetic atypical opioids as previously described for some of the substances [3]. The additional interaction with SERT may trigger serotonergic toxicity, especially in combination with other serotonergic drugs like SSRIs. This co-administration is frequent, thus awareness of this interaction is crucial.

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We have no conflict of interest to declare.

References

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[3] Codd EE et al. 1995, JPET; 274:1263-1270