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'Atypical' Antidepressants in Overdose

Clinical Considerations with Respect to Safety

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Abstract

The 'atypical' antidepressants comprise a heterogenous class with wide variation in presentation and management during overdose, both when compared with each other and with more traditional agents.

Further toxico-epidemiological data are required to make definitive predictions about the clinical effects of most of these agents in overdose. Here, however, we review the available information in a manner intended to benefit both prescribers and clinical toxicologists.

Our conclusion is that there can be no generic response by medical practitioners as to the 'safety' of these new antidepressants. Though undoubtedly exhibiting fewer problems in specific areas than some of the older classes of agents (e.g. arrhythmias with tricyclic antidepressants) each nonetheless presents unique safety problems.

We experienced great difficulty obtaining accurate information from the manufacturers about the animal toxicity data upon which their recommended human dose limits were set. This highlights the uncertainties involved with too readily making 'safety' claims about these agents.

The decision to prescribe 'atypical' antidepressant medications alleged to be both efficacious and safe in overdose involves a medicolegal tension. This tension is between respecting patient autonomy through frank communication of the material risk of overdose and non-disclosure to avoid such harm.

A patient's suicide attempt through overdose remains an inherent risk with any antidepressant prescription and one that will persist until significant remission occurs. It has been estimated that 25% of patients with major depression will attempt suicide and 15% will ultimately die by this means.[1] More recent data suggest the risk is much lower for most patients although still significant.[2] Many suicides will involve ingesting medications prescribed by their primary care physician.[3] The significance of the problem is highlighted by the fact that approximately 3% of adults in developed countries may exhibit suicidal ideation in any year.[4]

One means of calculating the relative overdose safety of an antidepressant involves comparison of whether a single ingestion of 14 times the therapeutic daily dose (the 14TD, a 2-week supply), produces a significant threat to life in an adult of average bodyweight and physical health.[5,6] Another important measure is the fatal toxicity index (FTI). This represents the deaths due to overdose with that agent per million prescriptions. Good correlations have been established between the FTI calculated using prescription numbers and other estimates of total drug users.[7]

Using such measures, tricyclic antidepressants (TCAs) appear to be associated with a greater risk of death in overdose than other antidepressant agents.[7-9] This finding has been confirmed by several studies using data on suicides from national government statistics, taking into account prescription rates published by official sources. Mortality, frequently from cardiac arrhythmias, can be produced by ingestion of most TCAs at 8–10 times the therapeutic dose (well below the 14TD).[10] The highest FTIs amongst the older antidepressants have been recorded for desipramine (FTI 201), amoxapine (FTI 93), dothiepin (FTI 53), amitriptyline (FTI 38) and tranylcypromine (FTI 44).[7]

It has been asserted that relative 'newness' in antidepressant development may be associated with decreased risk of toxicity in overdose.[11-14] Previously this claim was made for the selective serotonin reuptake inhibitors (SSRIs).[6,15] It has now been extended to include the heterogeneous class of new 'atypical' antidepressants which includes mirtazapine, venlafaxine, nefazodone and reboxetine.[14,16] Other widely used but older 'atypical' antidepressants include bupropion and the herbal remedy St John's Wort (*Hypericum perforatum*).

Some have asserted that the alleged relative safety of these 'atypical' antidepressants may have medico-legal implications in terms of prescribing practices.[14] Such a claim is undoubtedly controversial, particularly in so far as it downplays intra and inter-class variability in toxicity.[17]

Toxico-epidemiological data concerning the 'atypical' antidepressants in overdose remains incomplete.[18] Further, many trials of antidepressant agents do not report adequately on overdoses. In one review less than 10% of 315 antidepressant trials reported on suicides.[19]

There are many indications that the toxicity in overdose of some of the 'atypical' antidepressants may actually be comparable with the older agents, though with some significant differences in presentation and management. Our aim in this review is for each of these drugs to cover the pharmacology, toxicology and kinetics in so far as this might be reflected in overdose presentations, summarise clinical and forensic data on human toxicity and finally give practical advice about treatment.

1. Mirtazapine

1.1 Pharmacological and Toxicological Background

Mirtazapine is a potent presynaptic antagonist of central α-adrenoreceptors ($\alpha_2 >> \alpha_1$), promoting monoamine release (noradrenaline [norepinephrine] and serotonin [5-hydroxytryptamine; 5-HT]). Mirtazapine also acts as an antagonist at both 5-HT_2 and 5-HT_3 receptors. Therefore, the released 5-HT is believed to exert its effects primarily on 5-HT_1 receptors (although there are many other 5-HT receptors). Serotonergic adverse effects are unusual although significant adverse effects attributed to the serotonin syndrome have been reported, both in monotherapy and as a drug interaction with SSRIs.[20-23] Mirtazapine itself does not significantly inhibit noradrenergic or serotonergic re-uptake. However, it is a potent antihistamine leading to sedation and has weak anti-muscarinic activity.[24,25]

Mirtazapine is well absorbed in therapeutic doses and peak plasma concentrations are achieved in 2 hours. There is significant first-pass metabolism, mirtazapine is predominantly metabolised in the liver and is a substrate for cytochrome P450 (CYP) 1A2, 2D6 and 3A4. The elimination half-life ranges from 20 to 40 hours in therapeutic doses,[26] but there is no information on its kinetics in overdose.

Adverse effects in therapeutic doses include sedation, dry mouth, increased appetite and weight gain.[25] The highest recommended dose for mirtazapine is 45 mg/day although higher doses have been used in clinical trials.[25] The 14TD is thus 630mg. In mice studies the oral lethal dose $(LD)_{50}$ ranged from 600 to 720 mg/kg and in rats from 320 to 490 mg/kg. Subchronic (13-week) oral doses of 20 and 80 mg/kg in beagles showed vomiting, reduced motor activity and tremors but no mortality.[27] Attempts to obtain more detailed animal toxicity data from the manufacturer were unsuccessful.

1.2 Clinical Data on Overdose

There have been a small number (<20) of case reports of mirtazapine in overdose published.[13,27-33] Other than sedation, no major sequelae have been reported. One patient developed hypothermia after ingesting an overdose of mirtazapine.[32] Concentrations in reported cases have been up to 2300 μg/L,[29] (the recommended therapeutic range is 20–50 μg/L) and doses up to 1000mg,[27] without seizures or arrhythmias reported. An abstract of a German case series, based on follow-up of 73 overdoses where a Poisons Centre was consulted, reported no deaths and only one serious complication (an arrhythmia [not specified] after an overdose of 600mg). The maximum dose ingested in this series was 2250mg. Over half the patients remained asymptomatic.[34] A few deaths have been attributed by UK coroners to mirtazapine overdose. However, the FTI for mirtazapine is only 3.1 (95% CI 0.1–17.2). This is similar to that observed with SSRIs.[35]

1.3 Implications for Treatment of Overdose

The apparently low toxicity of mirtazapine in overdose is reassuring, but requires confirmation with more data from larger clinical series. No specific antidote exists for mirtazapine overdose and it is unlikely that any intervention is warranted in most patients. Patients who present within 1 hour of a very large ingestion (>1000mg) might be encouraged to drink activated charcoal. Patients should be observed for several hours.

It is possible that combined drug overdose with other serotonergic drugs (in particular monoamine oxidase inhibitors [MAOIs]) may give rise to more significant toxicity. Serotonergic toxicity may be mediated by 5-HT_2 or 5-HT_1 receptor effects.[36] It

has been reported to respond to serotonin antagonists. Drugs, such as chlorpromazine and cyproheptadine, that are commonly used to treat serotonergic toxicity are also predominantly 5-HT_2 antagonists, with 10- to 100-fold less affinity for 5-HT_1 receptors.[36] Mirtazapine itself is a potent 5-HT_2 antagonist.[37] Nonspecific supportive care (sedation, paralysis) may therefore be more appropriate for serotonergic toxicity arising from mirtazapine. This will be most likely to be required in mixed drug overdose and should be reserved for major symptoms (e.g. severe delirium, hyperthermia).

2. Venlafaxine

2.1 Pharmacological and Toxicological Background

Venlafaxine is a bicyclic antidepressant structurally and pharmacologically related to the non-opioid analgesic tramadol, but not to any conventional antidepressant medications. It is a racemate and has an active metabolite. The enantiomers of both the parent drug and the active metabolite inhibit monoamine uptake (serotonin > noradrenaline >> dopamine). Only at high doses is there a significant effect on noradrenaline uptake. It has no direct effect on serotonin, histamine, adrenergic or cholinergic receptors.[38] It does, however, have a dose-dependent blocking effect on sodium channels.[39]

Venlafaxine is most commonly available as an extended-release preparation. Absorption from the gastrointestinal tract is good but bioavailability at therapeutic doses is relatively low at 42%, due to high first-pass liver metabolism.[40] Peak plasma concentrations are achieved at 2 hours and at 6–7 hours for the extended-release preparation. Plasma concentrations during therapeutic use are approximately 30–70 μg/L.[41] The mean elimination half life of venlafaxine and its major active metabolite *O*-desmethylvenlafaxine are 5 and 11 hours, respectively.[41,42]

Adverse effects in therapeutic use are predominantly those attributable to serotonergic effects such as nausea, nervousness, dizziness, sweating, and insomnia. In addition dry mouth, hypertension and sedation are common.[43]

Attempts to obtain detailed animal toxicity data from the manufacturer were unsuccessful.

2.2 Clinical Data on Overdose

An early review of 14 cases of venlafaxine overdose proposed that this agent was safer than TCAs because sedation and tachycardia were the only significant symptoms.[44] However, even at that time it was becoming apparent that a number of fatal or life-threatening complications including hypotension, seizures and arrhythmias could occur in overdose.[45-48]

In therapeutic doses, venlafaxine has linear kinetics.[42] In overdose, very limited data suggest an increase in bioavailability and a prolonged half-life may occur, both presumably due to saturation of metabolic pathways.[47,48]

There are two substantial series of venlafaxine overdose, one of which has only been published as an abstract.[49,50] A detailed prospective clinical study of 51 sequential venlafaxine poisonings from a single centre found the common findings were seizures, serotoninergic toxicity, and minor ECG changes (QRS prolongation) with little or no anticholinergic or sedative effect. Venlafaxine in overdose was complicated by seizures frequently (14%) and much more often than in either SSRI or TCA overdose. The median dose in those who had a venlafaxine-associated seizure was 3150mg and the minimum dose was 900mg.[50] A larger study by the London centre of the UK National Poisons Information Service retrospectively followed up 632 (of 2954) enquiries about venlafaxine overdose. The majority of cases had only minor effects including sedation and tachycardia. Two patients had ventricular tachycardia but both recovered. Thirty (4.8%) cases had seizures (dose ingested 375mg to 10.5g). Seizures were mostly seen in those who ingested doses over 1.5g.[49] Thus, major toxicity can occur well below the 14TD of 2.1g. However, there does seem a reasonable margin of safety in the lower doses typical of paediatric ingestion. A retrospective series of 63 paediatric cases of venlafaxine overdose

noted the only toxicity was lethargy in one patient.[51]

Ventricular arrhythmias and cardiac arrest, presumably due to direct dose-dependent effects on cardiac conduction is the likely mode of death in fatal cases.[52,53] While QRS prolongation is quite common, another cardiotoxic effect reported in a few cases is significant corrected QT (QTc) interval prolongation (to 500 msec)[44,54] Fatal ventricular fibrillation was produced by an ingestion of 8.4g.[52] Other cases involving ventricular arrhythmias have also ingested very large (>7g) overdoses.[49,53] There are also a number of other fatal overdose cases where venlafaxine was the main or only implicated medication detected at autopsy.[45,46] The FTI for venlafaxine is significantly higher than the FTI of SSRIs, other 'atypical' antidepressants (data not available for bupropion or St John's Wort) and in the range of some of the less toxic TCAs at 13.2 (95% CI 9.2–18.5).[35]

2.3 Implications for Treatment of Overdose

The most commonly prescribed formulation of venlafaxine is an extended-release preparation, suggesting that gastrointestinal decontamination is likely to be effective even if presentation is delayed. A single dose of activated charcoal, followed by whole bowel lavage (polyethylene glycol solution) is generally appropriate for overdose of controlled-release preparations of toxic drugs.[55] However, this should bear in mind the high risk of sudden deterioration with seizures, and possible aspiration.

Toxic effects might be delayed in onset in extended-release venlafaxine overdose although the longest delay to onset of significant toxicity reported to date is only 15 hours.[50] Therefore, patients with extended-release overdose should be considered to be at risk of seizures for at least 18 hours, and for as long as they remain symptomatic. Seizures should be managed with airway protection and benzodiazepines. Repeated seizures are common but not status epilepticus. The use of sodium channel blocking drugs (e.g. phenytoin, carbamazepine) to control seizures might contribute to cardiotoxicity and these drugs are generally ineffective in drug-induced seizures. Therefore, high-dose benzodiazepines followed by barbiturates would be the preferred agents for refractory seizures.

Serotonergic toxicity is common and may respond to cyproheptadine.[56] The use of other proposed serotonin antagonists, which also have cardiac and proconvulsant effects (such as propranolol and chlorpromazine), would be unwise.

No specific antidote exists for venlafaxine-induced cardiac arrhythmias, although intravenous sodium bicarbonate and calcium appeared effective in one case.[53] Sodium bicarbonate would seem the preferred agent given it has much less toxicity, fewer contraindications and is accepted as effective in treating many other sodium channel blocking drugs.

3. Nefazodone

3.1 Pharmacological and Toxicological Data

Nefazodone is a phenylpiperazine derivative structurally and pharmacologically related to the older rarely used 'atypical' antidepressant trazodone. Its most potent effect is as an antagonist at postsynaptic $5HT_{2A}$ receptors. It is also a weak $5HT_{1A}$ receptor antagonist. It also weakly inhibits presynaptic reuptake of serotonin and to a much lesser extent noradrenaline and dopamine. It possesses some α_1-adrenergic blocking activity but no anti-muscarinic or antihistamine effects.[57,58] It has three active metabolites and the *in vivo* pharmacological effects suggest serotonin reuptake inhibition and $5HT_{2A}$ antagonism are the main effects in therapeutic use.[38]

Nefazodone has only 20% oral bioavailability due to extensive first-pass metabolism. It is metabolised in the liver to three active metabolites: hydroxy-nefazodone, desethyl hydroxynefazodone and m-chlorophenylpiperazine.[38] The mean plasma elimination half life of the parent drug in therapeutic doses is 2–4 hours but the half-life of the active metabolites is 2- to 10-fold longer.[43,59,60] It exhibits non-linear kinetics, the clearance being inversely proportional to the dose.[61] It is metabolised by and inhibits the enzymes CYP3A4 and CYP2D6. Clear-

ance may be reduced in CYP2D6 'poor metabolisers'.[60] There is no meaningful therapeutic plasma concentration as much of the therapeutic effect resides with the metabolites.

Attempts to obtain detailed animal toxicity data from the manufacturer were unsuccessful.

3.2 Clinical Data on Overdose

Nefazodone has no reports indicating significant toxicity in overdose. The largest study is a retrospective series of 1338 nefazodone-only overdoses reported to a poisons centre. The median ingested dose was only 250–300mg (range: 50mg to 13.5g) [the highest recommended dose is 600 mg/day and the 14TD is 8.4g]. Drowsiness (17.3%), nausea (9.7%) and dizziness (9.5%) were the most common symptoms. There was one seizure recorded in a patient with known epilepsy and there were no deaths. The median time to onset of symptoms was 1.75 hours and resolution time was 8–12 hours. Twenty-five percent of patients remained asymptomatic (median dose 250mg with range 75mg to 13.5g). Gastrointestinal decontamination was the most common treatment and no patients required intubation, ventilation or inotropes.[62] In other studies overdoses of 1g to 11.2g treated with gastrointestinal decontamination the only adverse effects were nausea, vomiting and somnolence.[63] The most serious report is an overdose of nefazodone 16.8g along with other drugs including a 'small amount' of verapamil in a 31-year-old female. The patient experienced increasing lethargy and slurred speech, bradycardia (42 beats/min) and hypotension (59/24mm Hg), prolonged QTc on the ECG and a decreased respiratory rate with low oxygen saturation (83%).[64] Concentrations of other ingested drugs were not reported and it seems likely that the most plausible contribution of the nefazodone was inhibition of the hepatic metabolism (via CYP3A4) of verapamil. Similarly, nefazodone might be expected to increase the bioavailability and prolong the half-life in mixed overdoses with other drugs primarily metabolised by CYP3A4 such as cisapride, carbamazepine, benzodiazepines and most other calcium channel blocking drugs.

There are a number of reports of serotonin syndrome from the combination of nefazodone and other drugs. None of these provide clear evidence of nefazodone causing a clinically severe serotonergic syndrome. For example, in the most serious case reported paroxetine and moclobemide were also involved and the nefazodone had been ceased for 48 hours.[65] In others relatively minor nonspecific symptoms were reported.[66-68] In perhaps the most interesting case a severe interaction with sodium valproate (a drug not usually regarded as serotonergic) was recorded.[69]

There are recent reports of life-threatening hepatotoxicity in therapeutic use.[70] However, to date there are no reports of hepatotoxicity after overdose to suggest this is a dose-related effect.

Despite significant use (576 000 prescriptions) there were no deaths recorded by the coroner between 1995 and 1999 in the UK as due to poisoning with nefazodone alone. The FTI for nefazodone is 0 (95% CI 0–6.4).[35]

3.3 Implications for Treatment of Overdose

Despite the limitations of the reports, the very low toxicity of nefazodone alone in overdose seems established. It is unlikely that any medical intervention is warranted in most patients. It is possible that combined drug overdose with other serotonergic drugs (in particular MAOIs) may give rise to more significant toxicity, although this has not been reported. However, nefazodone is a potent 5-HT_2 and a weak $5HT_{1A}$ antagonist, similar to chlorpromazine and cyproheptadine the commonly used serotonin antagonists.[36] Nonspecific supportive care (sedation, paralysis) may therefore be more appropriate than drug therapy for serotonergic toxicity in this instance. This will be most likely to be required only in mixed drug overdose and should be reserved for major symptoms (e.g. severe delirium, hyperthermia).

4. Reboxetine

4.1 Pharmacological and Toxicological Data

Reboxetine is a racemic mixture and both enantiomers are active. It is a selective noradrenaline reuptake inhibitor with minimal effect on serotonin and no effect on dopamine reuptake. It is chemically unrelated to other antidepressants and has low affinity for α-adrenergic and muscarinic receptors.[71]

Reboxetine is well absorbed with over 90% oral bioavailability. The main route of elimination is through metabolism by CYP3A4 in the liver. The elimination half life is 12 hours but may be longer in patients with liver disease.[72] Adverse effects in therapeutic doses do not suggest additional toxicological mechanisms.[71] A study in healthy volunteers noted no effects on the QT interval or other changes in the ECG at doses 2-fold higher than those used in therapy.[73]

Attempts to obtain detailed animal toxicity data from the manufacturer were unsuccessful.

4.2 Clinical Data on Overdose

The manufacturer has on file reports of a number of overdoses with no deaths or serious sequelae. Common effects of overdose were largely those one would expect from noradrenergic reuptake inhibition: sweating and tachycardia, anxiety, postural hypotension and hypertension. Individual patients have survived ingestions as high as 240mg[74,75] (recommended maximum daily dose is 10mg;[71] the 14TD is thus 140mg). The FTI of reboxetine is 0 (95% CI 0–21.1).[35]

4.3 Implications for Treatment of Overdose

The extremely limited data raise no specific concerns about the toxicity of reboxetine in overdose. A single dose of activated charcoal might be warranted if patients present very early after overdose. Severe hypertension should be treated with sedation, benzodiazepines and α-adrenergic antagonists as necessary.

5. Bupropion

5.1 Pharmacological and Toxicological Data

Bupropion is a monocyclic antidepressant whose primary mode of action is inhibition of neuronal uptake of noradrenaline and dopamine. It has minimal effects on reuptake of serotonin. Its chemical structure is similar to amphetamines; however, in therapeutic doses it has no stimulant effects in volunteers or patients with a history of amphetamine abuse.[76]

Bupropion was approved for use as an antidepressant in the US in 1986, but was withdrawn from the market because of a high incidence of seizures occurring at therapeutic doses.[77] It was reintroduced in 1989 with a lower recommended maximum dose of 450 mg/day.

Bupropion is well absorbed but has significant first-pass metabolism.[78] Peak plasma concentrations occur around 2 hours after ingestion of immediate-release preparations. However, bupropion is more commonly available in a sustained-release formulation.[79] Bupropion has a number of metabolites with significant pharmacological activity (hydroxybupropion and threohydrobupropion) with higher plasma concentrations and elimination half-lives approximately double that of the parent compound.[38,79] The major enzyme involved in biotransformation is CYP2B6, but bupropion may significantly inhibit CYP2D6.[80]

Published animal data demonstrated predominantly neurological toxicity in acute poisoning, concordant with human experience.[81] Despite reports of ECG abnormalities in human overdose (see section 5.2), bupropion has very low potency at blocking conduction *in vitro*.[82] Attempts to obtain more detailed animal toxicity data from the manufacturer were also unsuccessful in this instance.

5.2 Clinical Data in Overdose

The major manifestations in overdose with bupropion are neurological, in particular delirium and seizures are very common. In a retrospective case series involving 58 bupropion overdoses (mean

ingested dose 2.31g [immediate-release tablets]) the most common sequelae were neurological. Lethargy, tremors, vomiting and confusion were common. Seizures occurred in 21% from 1 to 8 hours post-ingestion (mean ingested dose 3.078g). Mixed overdoses with benzodiazepines did not have a lower incidence of seizures. There were no fatalities and sinus tachycardia was the only significant cardiovascular effect.[83]

However, cardiac complications and death in and out of hospital may also occur.[84-89] Ingestion of an overdose of 23g resulted in a generalised clonic seizure 2 hours post-ingestion with bradycardia and an asystolic arrest shortly thereafter associated with hypophosphataemia and hypokalaemia.[87] The 18-hour post-emergency department bupropion concentration was 446 μg/L and hydroxybupropion metabolite concentration was 3212 μg/L (the therapeutic range of plasma concentrations is 50–100 μg/L[90]). Ingestions of 1.5g and 9g have been associated with intraventricular conduction delays, the QTc in the first instance being 600msec 4 hours after ingestion and in the latter 485msec approximately 4 hours post-ingestion (QRS also 135msec).[85,91] Broad complex tachycardia and cardiac arrest in hospital have also been observed.[88,89]

Overdoses involving ingestion of bupropion <10g (producing post-mortem blood concentrations of 4 and 4.2 mg/L and total metabolite concentrations of 15 and 16.6 mg/L) have resulted in fatalities.[86]

The mean plasma concentration associated with seizures in therapeutic use is 170.4 μg/L (obtained 0.25–12.5 hours after the seizure).[92]

5.3 Implications for Treatment of Overdose

The most commonly prescribed formulation of bupropion is the sustained-release preparation, suggesting that gastrointestinal decontamination is likely to be effective even if presentation is delayed. Pharmacobezoar have been observed post mortem in fatal bupropion SR overdose (R. James, personal communication). A single dose of activated charcoal, followed by whole bowel lavage (polyethylene glycol solution) is generally appropriate for overdose of controlled-release preparations of toxic drugs.[55] However this should bear in mind the high risk of sudden deterioration with seizures, and possible aspiration.

Toxic effects may be delayed in onset, with the onset of seizures as late as 32 hours after ingestion of the sustained-release preparation.[93,94] Patients should be considered to be at risk of seizures for at least 18 hours, and as long as they are symptomatic.

No specific antidote exists for bupropion overdose. Seizures should be managed with airway protection and benzodiazepines. Repeated seizures are common but status epilepticus (although reported) is not.[93] The use of sodium channel blocking drugs (e.g. phenytoin, carbamazepine) to control seizures might contribute to cardiotoxicity. Therefore, high-dose benzodiazepines followed by barbiturates would be the preferred agents for refractory seizures.

6. St John's Wort (*Hypericum perforatum*)

6.1 Pharmacological and Toxicological Data

St John's Wort was originally thought to work due to the effect of the anthraquinone derivative hypericin irreversibly inhibiting MAO enzymes (B >A) in brain mitochondria.[95] Hypericin is present in low concentrations and this effect appears unlikely to be significant at therapeutic doses.[96,97] A broad range of flavonoids and phenols are also present, which may influence neurotransmitter uptake and adrenergic receptor density.[98] In particular, hyperforin is present in high concentrations and inhibits reuptake of dopamine, serotonin, noradrenaline, GABA and glutamate at concentrations that are achieved *in vivo*.[97] Despite this, dosage of this herbal extract is usually based on its hypericin content. This differs depending on the part of the plant used and growth conditions at varying times of the year.[99]

The bioavailability (of hypericin) is estimated to be 14–21% and the volume of distribution is around 20L in adults.[100] Kinetics are non-linear within the dosage range. The median elimination half-lives

after 250μg and 1500μg hypericin were approximately 24 and 48 hours, respectively.[100]

The maximum recommended daily oral dose is 900mg of an alcohol extract of hypericum (equivalent to 2700μg total hypericin). The 14TD is thus 12.6g. There is no clearly defined therapeutic range. Plasma concentrations of hypericin at therapeutic doses are generally <20 μg/L although in some individuals may be as high as 100 μg/L. Toxic serum concentrations are not established and cannot readily be determined. Attempts to obtain animal toxicity data from the manufacturer were also unsuccessful here.

6.2 Clinical Data on Overdose

We could find no reported cases of human overdose and no acute animal toxicity data. The suggestion has been made that St John's Wort, because it has fewer adverse effects than the older synthetic agents, is likely to be less toxic in overdose.[101] In a later study, the stated conclusion of the same authors was that its 'comparable efficacy to other antidepressants and its safety record' should lead St John's Wort to be a first-line treatment in the primary care setting.[102] Little specific work, however, has been done on the safety of hypericum extract in overdose.[103]

It would be hypothesised that the most likely adverse effects (on the basis of MAO inhibitor and catecholamine reuptake inhibitor effects) would be 'serotonin syndrome' or a catecholaminergic syndrome (tremor, hypertension, tachycardia).[104]

This would be expected to be more common with co-ingestion of other serotonergic or noradrenergic agents.[105] St John's Wort is an inducer of CYP enzymes (in particular CYP3A4) and thus might also theoretically increase the toxicity of other drugs such as paracetamol.[106] Hypertensive reactions seem plausible if indirect sympathomimetic agents are ingested.[107]

6.3 Implications for Treatment of Overdose

No specific antidote or management can be recommended for St John's Wort overdose. Standard supportive care and observation for at least 12 hours would be recommended until some clinical data become available to guide management. Activated charcoal should be administered if the patient presents within 1 to 2 hours of a significant ingestion. Serotonin or α-adrenergic antagonists may be considered if there are signs of a serotoninergic or catecholaminergic syndrome.

7. Conclusion: Relative Safety of the 'Atypical' Antidepressants in Overdose

While most of the 'atypical' antidepressants are clearly safer in overdose than TCAs, the clinical and animal data are much more limited than that available for SSRIs, which could be considered the current benchmark antidepressants in terms of safety in overdose. Moreover, it is difficult to make general conclusions about the relative safety in overdose of the 'atypical' antidepressants. First, ingestion of large amounts of venlafaxine, bupropion and mirtazapine have been reported to lead to fatalities. Second, although data on overdose using nefazodone, reboxetine and St John's Wort are relatively reassuring, they are also extremely limited. Third, the safety profiles are relatively distinct, and do not permit extrapolation between agents (table I). Fourth, such data as does exist are often reported in misleading ways to confirm the relative 'safety' in overdose.

The symptom profile of each of the above agents in overdose indeed seems quite different. Anxiety and confusion predominated in mirtazapine overdose. Somnolence and nausea characterised nefazodone overdose. Reboxetine caused an apparently benign sympathomimetic syndrome. St John's Wort overdose had insufficient data to develop a symptom profile in overdose. Hypotension and seizures were common after venlafaxine and bupropion overdose and both have lead to arrhythmias and a number of deaths.

Many claims that an 'atypical' agent is 'safe' in overdose arise from inconclusive data from a handful of cases. The FTI, though apparently indicating that most of the 'atypical' antidepressants are 'safer' than the TCAs, relies on assumptions that the drug classes are similar with respect to frequency of

Table I. Comparison of major features of the 'atypical' antidepressants relevant to toxicity in overdose

Drug	Maximum daily dose	Pharmacokinetics (in therapeutic use)	Common or serious effects reported in overdose	Fatal toxicity index[a] (95% CI)
Bupropion	450mg	Bioavailability ≈'low'; Vd ≈10–20 L/kg; delayed absorption with slow-release preparation; hepatic metabolism; $t_{1/2}$ ≈10h; 2 active metabolites ($t_{1/2}$ ≈20h)	Delirium, lethargy, tremor, vomiting, seizures, ECG changes tachyarrhythmias, death	NA
Mirtazapine	45mg	Bioavailability ≈50%; Vd ≈4.5 L/kg; hepatic metabolism; $t_{1/2}$ ≈20–40h; no active metabolites	Sedation	3.1 (0.1–17.2)
Nefazodone	600mg	Bioavailability ≈20%; Vd ≈ 0.5 L/kg; hepatic metabolism; non-linear kinetics; $t_{1/2}$ ≈2–4h; 3 active metabolites ($t_{1/2}$ ≈20–40h)	Sedation, nausea, dizziness	0.0 (0.0–6.4)
Reboxetine	10mg	Bioavailability ≈90%; Vd ≈0.5L/kg; hepatic metabolism; $t_{1/2}$ ≈12h	Sweating, tachycardia, anxiety, hypertension postural hypotension	0.0 (0.0–21.1)
St John's Wort (*Hypericum perforatum*)	900mg	Bioavailability ≈14–21%; Vd ≈20L (adult); non-linear kinetics; $t_{1/2}$ ≈24–48h	No data	NA
Venlafaxine	150mg	Bioavailability ≈42%; Vd ≈7 L/kg; t_{max} 6-7h with extended-release preparation; hepatic metabolism; $t_{1/2}$ ≈ 5h; 1 active metabolite ($t_{1/2}$ ≈11h)	Sedation, tachycardia serotoninergic symptoms, seizures, tachyarrhythmias, death	13.2 (9.2–18.5)

a Deaths per million prescriptions (from Buckley and McManus).[35]

NA = not available; $\mathbf{t_{1/2}}$ = elimination half-life; $\mathbf{t_{max}}$ = time to peak concentration; **Vd** = volume of distribution.

overdose, the amount taken in overdose and the risk profile of patients. Reputedly less toxic drugs are probably preferentially prescribed to patients at higher risk of poisoning and suicide.[108] Allegedly less toxic drugs are probably also less likely to be listed by the coroner as the sole cause of death.[35]

One fallacy behind allegations of 'safety' in overdose, particularly in the first few years of marketing, appears to involve the use of overgenerous assumptions to argue a large margin of safety. For example, the reliance on reported ingested dose in case reports (often ignoring contradictory pharmacokinetic data) or contrasting *peak* concentrations in overdose with therapeutic *trough* concentrations to imply that toxic effects were only observed with many-fold higher doses. This is an error that is so common in the published literature that it is inevitably perpetuated in reviews and by editors of toxicology textbooks.

For example, a case report of an overdose at approximately 18 times the maximum daily dose was alleged to indicate the 'safety of mirtazapine when taken in overdose'.[13] However, the report failed to acknowledge that the 6-hour blood concentration of the drug was only four times that expected from the maximum daily dose (206 vs 50 μg/L). It also stated that the patient developed anxiety and confusion, but did not provide information on the severity of these symptoms, including whether they required medication or lead to morbidity. The patient was admitted to an intensive care unit and received gastric lavage, laxatives and activated charcoal. This relatively aggressive treatment also makes any claim about the alleged 'safety' of the agent less convincing.

A plasma concentration of ten times the therapeutic concentration (530 μg/L) producing only lethargy and sinus tachycardia was similarly alleged to contribute to the data favouring 'safety' of mirtazapine in isolated overdose and to require no acute intervention other than 6 hours of observation. The report also notes, however, that 50g activated charcoal was given within 2 hours of ingestion.[33]

Another common error in reports allegedly demonstrating the 'safety' of these agents, is to state that overdose ingestion was significant at, for example, ten times the maximum plasma concentration achieved with an average daily dose, rather than the maximum daily dose.[109] Finally, initial data on toxicity in overdose often comes from a relatively

healthy population; for example, those in clinical trials who took overdoses and the young psychiatric patients who most commonly take overdoses. Data on toxicity in vulnerable populations (for example, those with hepatic, renal, respiratory or cardiac disease, epilepsy, the elderly or pregnant patients) are not systematically collected. We found no data on overdose with these drugs in any of these groups. This is analogous to the long delays in reporting of idiosyncratic adverse drug reaction only found in susceptible populations.

The best nonclinical indicator of fatal toxicity in humans is probably the LD_{50} in animal studies adjusted for the standard therapeutic dose.[7] These data are not readily obtainable in the standard product information for these drugs. Attempts to obtain this important information by direct request to the manufacturer were in each case unsuccessful.

As available evidence suggests that the older and newer antidepressants are equally efficacious, toxicity in overdose is frequently a major consideration in the prescribing decision. Some have suggested that failure to prescribe safer 'new' antidepressants may constitute medical negligence.[14] Moreover, it may be difficult to involve the patient in this decision as accurate description of the material risks of drug overdose may increase the likelihood of its occurrence.[110] However, the risk of overdose in depressed patients is common enough to make it reasonably likely and so required by law in many countries to be disclosed to all patients. Doctors may not be protected in either medical ethics or law if they attempt to withhold this information from patients on the basis that it might increase the risk of harm to them ('therapeutic privilege'). The only satisfactory solution to this dilemma is to generally prescribe antidepressants that a reasonably competent member of the profession would consider proven to be safe in overdose. A deluge of 'safety' allegations in the medical literature may be insufficient if each is based on flawed assumptions. This is compounded by the difficulty in obtaining accurate animal toxicity data from the manufacturers. Preclinical toxicity data should be more readily accessible, particularly if relative 'safety' in overdose is a marketing strategy for these drugs.

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