

A Review of Serotonin Toxicity Data: Implications for the Mechanisms of Antidepressant Drug Action

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Data now exist from which an accurate definition for serotonin toxicity (ST), or serotonin syndrome, has been developed; this has also led to precise, validated decision rules for diagnosis. The spectrum concept formulates ST as a continuum of serotonergic effects, mediated by the degree of elevation of intrasynaptic serotonin. This progresses from side effects through to toxicity; the concept emphasizes that it is a form of poisoning, not an idiosyncratic reaction. Observations of the degree of ST precipitated by overdoses of different classes of drugs can elucidate mechanisms and potency of drug actions. There is now sufficient pharmacological data on some drugs to enable a prediction of which ones will be at risk of precipitating ST, either by themselves or in combinations with other drugs. This indicates that some antidepressant drugs, presently thought to have serotonergic effects in animals, do not exhibit such effects in humans. Mirtazapine is unable to precipitate serotonin toxicity in overdose or to cause serotonin toxicity when mixed with monoamine oxidase inhibitors, and moclobemide is unable to precipitate serotonin toxicity in overdose. Tricyclic antidepressants (other than clomipramine and imipramine) do not precipitate serotonin toxicity and might not elevate serotonin or have a dual action, as has been assumed.

Key Words: Serotonin toxicity, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, mirtazapine, moclobemide

Serotonin toxicity (ST), often referred to as serotonin syndrome (SS), is an iatrogenic drug-induced "toxidrome" (a contraction of the words toxic and syndrome). Toxidromes consist of groups of signs and symptoms found together with a particular type of poisoning. Serotonin toxicity displays the characteristics expected of a synaptic serotonin concentration-related phenomenon. The term ST is preferable because it is more informative than SS. It has been pointed out that the term SS insinuates an idiosyncratic reaction, like neuroleptic malignant syndrome. This promotes misconceptions that have widespread and sometimes serious consequences. We have been struggling to recognize and understand ST for 50 years, since the first report (Mitchell 1955) and the first proposed explanation of the mechanism of raised intrasynaptic serotonin (Oates and Sjoerdsma 1960). It is an important phenomenon because potentially fatal combinations of therapeutic drugs are still being prescribed or accidentally combined and because there is misunderstanding about what drugs are able to precipitate it, the symptoms, the pathophysiology, and the treatment. It is a complex topic that spans many disciplines, and single reviews cannot provide a full perspective. Some other recent reviews are recommended (Boyer and Shannon 2005; Dunkley et al 2003; Gillman 1998, 1999, 2004b, 2005a; Gillman and Whyte 2004; Isbister and Hackett 2003; Isbister et al 2003b, 2004; Nisijima et al 2001, 2003; Parrott 2002; Shioda et al 2004; Whyte 2004b, 2004d, 2004e; Whyte et al 2003).

Serotonin toxicity is one of the rare instances of drug interaction in clinical medicine whereby death can result from a single dose of a drug when errors are made, especially when no specific treatment is given, as exemplified by a recent death in a teaching hospital (Otte et al 2003). The term SS continues to be used, sometimes imprecisely, to describe varying degrees of severity of side effects (Ubogu and Katirji 2003) from drugs that

do not, and cannot, cause ST (Gillman 2003c; Isbister and Whyte 2003). Such erroneous reports are still being published in prominent journals (Haddow et al 2004) and continue to maintain the confused and inaccurate understanding of this toxidrome (Gillman 2005b; Isbister and Buckley 2005). At the other extreme, cases of life-threatening ST, precipitated by ingestion of both monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) together, are not always receiving the urgent and aggressive medical intervention that their predictably serious consequences demand; these more severe reactions are predicted by the spectrum concept of ST. We now know from Whyte's data that 25% of overdoses involving combinations of moclobemide and SSRIs will result in life-threatening ST; the danger with the old MAOIs and SRIs is even higher.

Professor Whyte's research group at the Hunter Area Toxicology Service (HATS) in Newcastle, Australia, has maintained a prospective clinical database of all poisonings since 1987. The evidence from the HATS series of 2222 serotonergic overdoses has been published in a seminal series of articles (Dunkley et al 2003; Isbister and Hackett 2003; Isbister et al 2003a, 2003b; Whyte 2004a, 2004d, 2004e; Whyte et al 2003). The availability of these data means that unsystematic and incomplete observations from individual case reports are unlikely to be of much further value.

The HATS data indicate that it is only the higher elevations of serotonin resulting from MAOI plus SRI combinations that are likely to induce hyperpyrexia and death. The HATS data also provide information on the relative frequency and severity of toxicity with different drugs, and this information is useful in refining hypotheses about the actions of the drugs. These data consolidate the spectrum concept of ST; the strong evidence supporting the existence of a clear "dose-effect" relationship, mediated by the degree of elevation of intrasynaptic serotonin, is illustrated by the data in Table 1 and has been elaborated elsewhere (Gillman 1998; Isbister et al 2004; Whyte 2004d, 2004e; Whyte et al 2003). There is a strong correlation between various different drugs' ability to raise serotonin levels in microdialysis studies in rats and the appearance of signs of ST in both rats and humans.

The typical clinical features of ST in humans, derived from the HATS data (Gillman and Whyte 2004; Isbister et al 2003b; Whyte 2004d; Whyte et al 2003) are 1) neuromuscular hyperactivity: tremor, clonus, myoclonus, and hyperreflexia, and, in the advanced stage, pyramidal rigidity; 2) autonomic hyperactivity: diaphoresis, fever, tachycardia, tachypnea, and mydriasis; and 3) altered mental status: agitation and excitement, with confusion

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Table 1. Comparative Degree of Serotonin Elevation by Different Drugs in Relation to ST

Drug (Reference)	ST Humans	ST Rats	5-HT Levels (Rats) ^a
MAOI + SRI (Salter et al 1995; Shioda et al 2004)	Severe ^b	Severe ^b	10,000
MAOI + L-tryptophan (Sleight et al 1988)	Moderate	Moderate/severe	1500
MAOIs (Nisijima et al 2003)	Moderate/severe ^b	Moderate/severe	1000
Moclobemide + MDMA (Freezer et al 2005)	Severe ^b	Severe ^b	1000
MDMA (Freezer et al 2005; Gough et al 2002; Mechan et al 2002)	Moderate	Moderate	500
SSRIs (Felton et al 2003; Mork et al 2003; Salter et al 1995)	Mild/moderate	Mild	300
Venlafaxine (Koch et al 2003; Weikop et al 2004)	Moderate	No known data	300
Moclobemide (Iurlo et al 2001)	None	None	150
TCA (Felton et al 2003)	None	None	125
Mirtazapine (Bengtsson et al 2000; de Boer et al 1996; Devoto et al 2004; Nakayama et al 2004)	None	None	120

ST, serotonin toxicity; 5-HT, 5-hydroxytryptamine (serotonin); MAOI, monoamine oxidase inhibitor; (S)SRI, (selective) serotonin reuptake inhibitor; MDMA, 3,4-methylenedioxymethamphetamine ("Ecstasy"); TCA, tricyclic antidepressant.

^aApproximate percent increase above baseline in microdialysis studies. The precision of comparability between different studies is uncertain.

^bSevere indicates fatalities are definitely expected.

in the advanced stage only. Descriptions of the general clinical presentation of patients can be found elsewhere (Boyer and Shannon 2005; Gillman and Whyte 2004; Whyte 2004d). Whyte et al have applied classification and regression tree rules to their large data set and found "... only clonus (inducible, spontaneous or ocular), agitation, diaphoresis, tremor and hyperreflexia were needed for accurate prediction of ST as diagnosed by a clinical toxicologist." These rules are detailed in their seminal article (Dunkley et al 2003). They demonstrate clearly that if, in the presence of a serotonergic agent, the single sign of spontaneous clonus is present, then ST might be reliably diagnosed.

The Spectrum Concept of ST

Whyte, Gillman, and colleagues have elaborated the spectrum concept of ST, with data from overdoses in humans (Dunkley et al 2003; Gillman 1997; Gillman and Whyte 2004; Isbister et al 2003b; Whyte and Dawson 2000). This is substantiated by research in animals reviewed elsewhere (Gillman 1998), in which serotonin levels have been elevated to a greater extent, producing more severe ST, by administration of combinations (e.g., MAOI plus L-tryptophan and MAOI plus SRI) than with single drugs (Table 1). The spectrum concept formulates ST as a progression of serotonergic effects mediated by the degree of elevation of intrasynaptic serotonin. These range from serotonin-related side effects (at therapeutic doses) through to toxicity and culminate in death with MAOI/SRI combinations. Serotonin concentrations become sufficiently elevated to cause severe toxicity (of a life-threatening degree) most commonly when combinations of MAOIs and SRIs, or MAOIs and serotonin releasers (e.g., amphetamine) are co-administered.

The evidence from the HATS database indicates that in humans serotonergic signs become progressively more severe with increasing dose of an SSRI and that approximately 15% of people who have taken an SSRI-alone overdose develop a moderate degree of severity of ST that will result in admission to a hospital and medical treatment. Overdoses of SSRIs alone do not usually result in severe ST or pyrexia in excess of 38.5°C (Isbister et al 2004). Indeed, only one patient in Whyte's series of 469 cases developed a temperature in excess of 38.5°C, and there is only one case report in the known literature of an apparent SSRI-alone overdose causing more severe ST (temperature 40°C) (Olsen et al 2004). This suggests a ceiling effect on serotonin elevation for SSRIs.

Implicated Drugs

Understanding ST as a form of poisoning and taking the spectrum concept into consideration demonstrates the importance of knowing the degree to which different drugs are capable of elevating brain serotonin (Table 1). Bayesian reasoning further elucidates this issue by emphasizing the importance of prior knowledge of the ingested drug in assessing the likelihood, severity, and type of poisoning (i.e., the toxidrome characteristic of a class of drugs) (Buckley et al 2002; Gill et al 2005). Whyte's HATS data demonstrate that approximately 50% of patients who have ingested mixtures of moclobemide and SRIs will exhibit moderately severe ST; ingestion of such mixtures is the strongest predictor of severe ST.

The three important mechanisms, in relation to severe ST, are inhibition of reuptake, presynaptic release, and MAO inhibition. The therapeutic drugs so far implicated in severe reactions that are capable of precipitating fatalities are the combination of MAOIs with either SRIs or the only clinically available serotonin releaser, amphetamine. Fenfluramine is no longer available in most countries, and methylphenidate is not serotonergic: it does not elevate extracellular serotonin in rats (Kuczenski and Segal 1997). A recent review of the human literature suggests that, of the releasers, amphetamine is a risk for ST with MAOIs, whereas methylphenidate is not (Feinberg 2004). Amphetamine has potency as a releaser, and methylphenidate does not (Rothman and Baumann 2003). The illicit drug MDMA (3,4-methylenedioxymethamphetamine; Ecstasy) is a releaser and has the potency to precipitate fatalities with MAOIs (Vuori et al 2003). The effect of MDMA is diminished by SRIs because they impede its uptake into the presynaptic terminal, which prevents the releaser effect (Mechan et al 2002).

There are some SRIs and MAOIs that doctors might not readily recognize (e.g., sibutramine, imipramine, tramadol, meperidine (pethidine), chlorpheniramine, and linezolid). The degree of risk with the new antibiotic linezolid is currently uncertain because of limited data concerning its MAOI potency (Gillman 2003b), but it is currently clear that it is capable of inducing ST (with SRIs). It is therefore essential to have an accurate table of drugs with information about the degree to which they are capable of elevating serotonin. Tables 1 and 2 show this information for therapeutic drugs.

Despite advances in pharmacology, there are still areas of uncertainty; serotonin releasers, usually termed "indirectly acting

Table 2. Serotonergic Drugs

Serotonin Reuptake Inhibitors (Selective and Nonselective)	
Paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram	
Venlafaxine, milnacipran, duloxetine, sibutramine	
Clomipramine, imipramine	
Tramadol, meperidine (pethidine), fentanyl, methadone, dextromethorphan, dextropropoxyphene pentazocine	
Chlorpheniramine, brompheniramine	
Serotonin Precursors	
5-hydroxytryptophan L-tryptophan	
5-HT _{1A} Antagonists	
LSD, dihydroergotamine, bromocriptine, buspirone	
Serotonin Releasers	
Amphetamine MDMA	
MOAIs	
Tranylcypromine, phenelzine, nialamide, isoniazid, iproniazid, isocarboxazid	
Pargyline, selegiline (deprenyl), clorgyline, furazolidone, procarbazine, linezolid	
Moclobemide	

5-HT, 5-hydroxytryptamine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine ("Ecstasy"); MAOI, monoamine oxidase inhibitor. Fatalities from serotonin toxicity involving analgesics have been with meperidine (pethidine), tramadol, dextromethorphan, and fentanyl. Methylphenidate has been removed from the table because evidence now indicates that it does not have significant serotonergic potency. Data from Gilman (2005c).

sympathomimetic" drugs, have until recently had no assay to measure their potency, and uncertainty has remained about the interactions and mode of action of some. The lack of information concerning the serotonergic potency of opioid analgesics remains a prominent area of incomplete data. Monoamine oxidase inhibitor opioid interactions have been reviewed; some opioids might not act as reuptake inhibitors at all but as releasers (Gillman 2005a). There are few data other than that in Codd's article (Codd et al 1995; Toll et al 1998) and none at all regarding their possible releaser potency.

Serotonin Toxicity in Relation to Mechanisms and Potency of Drug Actions

Tricyclic Antidepressants

For the structurally homologous tricyclic antidepressants (TCAs), the relationship between SRI potency and the ability to precipitate fatalities in combination with MAOIs is robust. The

TCAs exhibit affinities at the human cloned serotonin transporter that vary 1000-fold (Table 3). There has been discussion regarding which TCAs have significant effects on serotonin levels and whether amitriptyline exhibits clinically relevant dual effects (Freemantle et al 2000; Thase 2003). Some evidence suggesting that it does not has recently been summarized (Gillman 2003a). Thus, ST data provide insights into what might constitute meaningful serotonergic potency (cf. mirtazapine and mianserin [Gillman 2003c, 2004a] and opioid analgesics [Gillman 2005a]). It is safe to combine amitriptyline with an MAOI without precipitating serotonergic side effects or ST (Gillman 1998). If an overdose of amitriptyline is taken, ST symptoms do not occur (Dawson 2004). Other TCAs with weaker SRI potency than amitriptyline are not associated with ST, either in overdose by themselves or when combined with MAOIs (Gillman 1998, 2003a; Whyte 2004c). Conversely, the more potent TCA SRI clomipramine has both clinically relevant serotonergic effects (efficacy in obsessive-compulsive disorder, which other TCAs do not possess) and serotonergic effects in overdose (Whyte and Buckley 1995). Clomipramine is able to cause marked serotonergic side effects and ST, as well as fatalities from ST if combined with MAOIs (Amsterdam et al 1997; Gillman 1998; Oefele et al 1986). These data give an indication of what constitutes clinically meaningful SRI potency in terms of K_i values (Table 3).

SSRIs (and Venlafaxine)

The HATS data demonstrate that approximately 15% of overdoses of an SSRI alone exhibit moderate ST and that overdoses of SSRIs do not cause life-threatening ST or pyrexia in excess of 38.5°C, indicating a probable ceiling effect. Table 3 shows that venlafaxine is possibly anomalous, because its SRI potency, at K_i 7.5–100 nmol/L, is less than amitriptyline (2.8–36 nmol/L), so it might be expected to have a lesser risk for ST; however, it precipitates ST even more frequently than SSRIs (30% vs. 15%; Whyte and Dawson 2000). There is evidence suggesting that it might act other than as an SRI (Bamigbade et al 1997; Beique et al 1998); if that is so, it would be consonant with this discrepancy. There could be imprecision with the correlation between these assays and actual SRI effects, and factors such as relative dose and tissue levels might explain the difference. Clomipramine overdose results in ST less frequently than SSRIs, perhaps because of its significant potency at serotonin 2A (5-HT_{2A}) receptors; but it can still cause marked serotonergic side effects at therapeutic doses (Lejoyeux et al 1993). One possible explanation is that the ceiling for 5-HT_{2A} antagonist effects is higher than

Table 3. ST and K_i s of Some Antidepressants at the 5-HT Transporter

Drug	K_i (nmol/L)	ST + MAOIs	ST (overdose)
SSRIs	0.13–2.2	Frequent fatalities	15%
Clomipramine	0.14	Frequent fatalities	5%
Imipramine	1.3–20	Intermediate, fatalities	Rare
Amitriptyline	2.8–36	None, no fatalities	None
Other TCAs	> 100	None, no fatalities	None
Venlafaxine	7.5–102 ^a (anomalous)	Frequent, fatalities	30%
Trazodone	252–690	None, no fatalities	None
Nefazodone	460–550	None, no fatalities	None
Mianserin	1000–10,000 ^b	None, no fatalities	None
Mirtazapine	100–8000 ^b	None, no fatalities	None

ST, serotonin toxicity; 5-HT, 5-hydroxytryptamine; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor. The data in this table are extracted from <http://pdsp.cwru.edu/pdsp.asp> (Roth et al 2000).

^aWhere more than one value is available (e.g., venlafaxine) the range is given. All the data are from assays using human cloned receptors, except mianserin and mirtazapine (see note).

^bRat brain.

for SRI action, so 5-HT_{2A} antagonism predominates and reduces ST only when an overdose has been taken. Amitriptyline has potency at 5-HT_{2A} receptors similar to clomipramine but does not cause marked serotonergic side effects at therapeutic doses or ST in overdose. This suggests that weaker SRI potency, rather than 5-HT_{2A} antagonism, might account for the absence of ST with amitriptyline/MAOI combinations.

It has been suggested that the risk of inducing ST might be higher with serotonin norepinephrine reuptake inhibitors than with SSRIs, especially when these are combined with a 5-HT_{1A} antagonist (Bjorvatn et al 2000). As more human toxicology data accumulate, it might be possible to address questions of relative toxicity. Data on the relative risk with milnacipran, sibutramine, and duloxetine will be interesting, but in view of the lack of systematic human toxicology research, sufficient data are unlikely to be available for some time.

Moclobemide and Irreversible MAOIs

Moclobemide, a reversible competitive selective MAO-A inhibitor, does not precipitate ST in overdose by itself, nor does it produce serotonergic side effects in clinical use. It is only implicated in ST if it is combined with a drug that has significant SRI or releaser potency (Isbister et al 2003b). Isbister's case series of 106 moclobemide overdoses from the HATS database revealed neither ST nor serotonergic signs in cases where moclobemide alone or moclobemide plus another nonserotonergic drug had been ingested (85 cases). In the 21 cases where it had been ingested in combination with a serotonergic drug, however, 50% of cases exhibited ST, even though the other serotonergic drug had often been ingested only in therapeutic quantities, not as an overdose. In 6 of these 21 cases, severe ST developed with temperature >38.5°C and muscle rigidity, requiring intubation, paralysis, and 5-HT_{2A} antagonists.

These effects are consonant with moclobemide's low potency to elevate serotonin levels in rats (Table 1). The degree of elevation of serotonin with moclobemide is substantially less than with SSRIs, and the relationship between this and serotonergic side effects is clear. The old irreversible nonselective MAOIs, such as tranylcypromine, cause definite ST in overdose, exhibiting hyperpyrexia and fatalities (Whyte 2004a). This again fits with their greater ability to elevate serotonin levels in rats. The correlation between these variables with different classes of drugs is summarized in Table 1, which shows that order of magnitude effects are predictable for different types of drugs and combinations with different mechanisms of action (SSRIs, MAOIs and releasers).

In contrast to modest antidepressant effects in clinical trials, clinical experience and some trials suggest that moclobemide might have a weaker antidepressant effects than other antidepressants (Danish University Antidepressant Group 1993). One of the possible interpretations of this is that greater elevations of serotonin than moclobemide is able to produce are required for optimal antidepressant effects. Such observations might help to clarify the degree of elevation of serotonin levels that is required to help depression.

Some reviews have suggested that moclobemide is a safe and viable treatment when combined with SSRIs (Bonnet 2003; DeBattista et al 1998). The risks of such combinations have been summarized (Gillman 2004b). The data in Table 1 suggest the probability that the degree of elevation of serotonin with the combination is such that toxicity might be expected. Several preliminary studies of combining moclobemide with SSRIs were published nearly 10 years ago, the largest being by Hawley

(Hawley et al 1996). Hawley decided to stop his research because of high levels of moderately severe serotonergic side effects, especially with moclobemide plus venlafaxine. A detailed account of interactions between moclobemide (and other MAOIs) and SRIs is available (Gillman 2005c). No further research has been reported since, and no double-blind trials have been published, so there is currently no controlled evidence to support the antidepressant efficacy of this type of combination. In summary, these results suggest that the degree of elevation of serotonin produced by moclobemide alone is insufficient for optimal antidepressant efficacy, but that the greater elevations caused by combining it with SSRIs can produce higher levels that can sometimes be excessive; unfortunately, the degree of antidepressant effectiveness of these combinations remains uncertain. These interactions are complex, especially when pharmacokinetic factors influence drug levels, which then have further pharmacodynamic interactions. The misunderstanding of drug interactions played a part in the demise of mixed treatment regimens using the old MAOIs plus TCAs (Gillman 1998; Gillman and Whyte 2004). Adequate trials of these various combinations have not been undertaken, so valuable data concerning potentially effective treatments might remain undiscovered. Sargent's words from 40 years ago are still worth noting: "We are never going to learn how to treat depression in an MRC statistician's office" (Sargent 1965). Most current antidepressant agents produce small improvements that require clarification with statistics, but only because the clinical effect is small. Sargent meant that when the treatment effect is large, statistics become a refinement rather than a necessity.

The older irreversible MAOIs do exhibit greater potency for inducing ST, but there are no systematic data on the comparative risk versus moclobemide. There is no doubt that MAOI-alone overdoses are more dangerous than moclobemide-alone overdoses (see Table 1). The limited case series available give a strong indication of greater toxicity, and these data have been reviewed elsewhere (Gillman 1998). Also, clinical experience and extrapolation from the animal evidence available makes it almost certain that they are substantially more prone to precipitate ST.

Other Antidepressants

Trazodone and nefazodone are primarily 5-HT_{2A} antagonists, although their mechanism of antidepressant action, if any, is uncertain. They neither exhibit serotonergic side effects nor induce signs of ST in overdose alone (Isbister and Hackett 2003). The absence of ST when they are combined with MAOIs indicates that they have no clinically significant SRI potency (Table 1) and probably do not significantly elevate serotonin levels by any mechanism (Gillman 2003c, 2004a). They might have weak antidepressant effects and are rarely used as first-line treatment: trazodone is used as a hypnotic, and nefazodone has now been withdrawn.

Mirtazapine has been described and marketed as a noradrenergic and specific serotonergic antidepressant and has been presumed to have dual action (Blier 2001; Gupta et al 2003; Montgomery 1999; Tran et al 2003); however, this assumption is predicated on animal experiments that have demonstrated either small increases in serotonin (and norepinephrine) or no increase at all (Bengtsson et al 2000). Selective SRIs increase extracellular serotonin to a greater degree (see Table 1). Consideration of mirtazapine in relation to ST demonstrates that it neither exhibits serotonergic side effects nor induces signs of ST in overdose (Buckley and Faunce 2003). In addition, the apparent absence of

ST when mirtazapine is combined with MAOIs suggests that it has no significant serotonergic effects.

Toxicity Data

Toxicity data are infrequently published and might be unavailable to researchers outside the industry (Buckley and Faunce 2003). Median lethal dose data would assist significantly in assessing the relative degree of ST exhibited, and especially in indicating whether it is possible for any of these drugs to cause ST fatalities in rats. Systematically collected toxicity data from cases of overdoses of drugs in humans are not recorded or collated on a large scale or national basis; the HATS database seems to be unique.

Conclusion

Serotonin toxicity has now been a clinical problem for 50 years. The progress made in understanding it and the implementation of that knowledge into clinical teaching and practice reflects many factors, among which is the difficult and complex interdisciplinary nature of the topic. It is a drug-induced manifestation of raised intrasynaptic serotonin; therefore, the degree of severity and risk of fatality is related to the extent of serotonin elevation, which depends on the potency and admixture of the serotonergic drugs precipitating it (Table 1). It is a sine qua non that a drug must be capable of large elevations of serotonin if it is to induce ST; drugs like moclobemide and mirtazapine do not elevate serotonin sufficiently and ipso facto cannot cause ST.

There is room for further work in the area of postmarketing surveillance and human toxicology, but these must be systematically collected data: individual case reports have hindered rather than helped understanding in this field. This incompleteness of published drug toxicity and interaction data is impeding research. This article attests to the importance of studies on ST, which will help to improve understanding of both the mechanisms of drug action and disease pathophysiology. Their value for drug research and development might be underrecognized. Some antidepressant drugs presently assumed to have serotonergic effects, such as mirtazapine and moclobemide, might have insufficient potency to induce optimal effects in humans.

There is also a gap in the literature resulting from the paucity of experimental animal data, and there is much information to be obtained that would be of value when fed back into models of drug action.

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