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The serotonin syndrome and its treatment

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Serotonin syndrome is caused by drug induced excess of intrasynaptic 5-hydroxytryptamine. The clinical manifestations are mediated by the action of 5-hydroxytryptamine on various subtypes of serotonin receptors. There is no effective drug treatment established. The history of the treatment of serotonin syndrome with 5-hydroxytryptamine blocking drugs is reviewed. A literature search was undertaken using both Medline and a manual search of the older literature. Reports of cases treated with the 5-HT_2 blockers cyproheptadine and chlorpromazine were identified and analysed. There is some evidence suggesting the efficacy of chlorpromazine and cyproheptadine in the treatment of serotonin syndrome. The evidence for cyproheptadine is less substantial, perhaps because the dose of cyproheptadine necessary to ensure blockade of brain 5-HT_2 receptors is 20–30 mg, which is higher than that used in the cases reported to date (4–16 mg).

Key words: chlorpromazine; cyproheptadine; serotonin antagonists; serotonin syndrome; treatment

'What experience and history teach is this — that people and governments never have learned anything from history, or acted on the principles deduced from it' (Georg Wilhelm Hegel)

Introduction

Serotonin syndrome (SS) is caused by drug induced excess of intrasynaptic 5-hydroxytryptamine (5-HT). The clinical manifestations are mediated by the action of 5-HT on various subtypes of serotonin receptors. Cases of probable SS found in the literature that were treated with the 5-HT receptor blockers chlorpromazine or cyproheptadine are reviewed. Of all the cases of SS identified, only these were treated with chlorpromazine or cyproheptadine. The response to treatment is estimated from the limited data available in these reports.

There have been about 23 deaths from SS reported in the medical literature in the last 10 years, not including those associated with 3,4-methylenedioxymethamphetamine (MDMA) toxicity (Tackley and Tregaskis, 1987; Brennan *et al*., 1988; Kline *et al*., 1989; Stern *et al*., 1992; Beasley *et al*., 1993; Neuvonen *et al*., 1993; Nimmo *et al*., 1993; Braitberg, 1994; Keltner, 1994; Hernandez *et al*., 1995; Power *et al*., 1995) and it is likely that other deaths have occurred about which no account has been published. None of the deaths reported in the literature occurred during the treatment of depressive illness with irreversible monoamine oxidase inhibitors (MAOIs) combined with tricyclic antidepressants (TCAs), i.e. mixed or combined antidepressant treatment. This is probably because the TCAs that exhibit greater serotonin reuptake inhibitor activity, in therapeutic dosages, have rarely been used therapeutically with MAOIs. The most potent serotonin reuptake inhibitors of the TCAs are clomipramine (CMI) and imipramine (IMI) (Richelson, 1984) and when they have been combined with MAOIs, in overdose or accidentally, they have often caused SS.

Background

There were reports of SS from animal research starting in 1958 (Bogdanski *et al*., 1958; Horita and Gogerty, 1958; Hess *et al*., 1959; Hess and Doepfner, 1961; Himwich and Petersen, 1961; Himwich, 1962; Curzon *et al*., 1963; Nymark and Moller Neilsen, 1963; Loveless and Maxwell, 1965; Rogers and Thornton, 1969; Penn and Rodgers, 1971; Fahim *et al*., 1972; Sinclair, 1973; Green and Grahame-Smith, 1976; Jounela *et al*., 1977; Felner and Waldmeier, 1979; Fjalland, 1979; Marsden and Curzon, 1979) and these continued to accrue until the seminal papers of Marley (Marley and Wozniak, 1983; Marley and Wozniak, 1984a,b; Marley and Wozniak, 1985), usually without percolating through to the corpus of psychiatric literature. These early studies indicated that some neuroleptics lessen symptoms of SS in animals (Bogdanski *et al*., 1958; Himwich and Petersen, 1961; Sinclair, 1973; Green and Grahame-Smith, 1974; Marley and Wozniak, 1984b) and that the hyperactivity syndrome which was seen when some analgesics were given in combination with MAOIs was related to excess intra-synaptic 5-HT. Subsequent work has shown that meperidine and dextromethorphan have, in addition to their other properties, serotonin reuptake inhibitor activity (Carlsson *et al*., 1969; Carlsson and Lindqvist, 1969; Sinclair, 1973). Many MAOI/analgesic reactions have been recorded in humans and these have occurred only with analgesics that have serotonin reuptake inhibitor activity (Mitchell, 1955; Papp and Benaim, 1958; Palmer, 1960; Shee, 1960; Cocks and Passmore-Rowe, 1962; Denton *et al*., 1962; London and Milne, 1962; Taylor, 1962; Vigran, 1964; Pollock and Watson, 1971; Sovner and Wolfe, 1988; Hansen *et al*., 1990; Zornberg *et al*., 1991;

Zornberg, 1993; Jahr *et al*., 1994; Mason and Blackburn, 1997). Even moclobemide (MOC), a selective reversible inhibitor of MAO-A (RIMA) with a very short half-life, has been implicated in producing SS in therapeutic dosages, both with relatively weaker serotonin reuptake inhibitors such as IMI (Brodribb *et al*., 1994), meperidine (Gillman, 1995), fluoxetine (Benazzi, 1996; Liebenberg and Berk, 1996), and more potent serotonin reuptake inhibitors such as paroxetine (Robert *et al*., 1996). It is likely that the risk of SS with MOC is much lower than with MAOIs.

The present state

There is no established definition of the diagnostic features of SS; indeed, it is not a discrete entity with diagnostic features (Hilton *et al*., 1997; Lane and Baldwin, 1997). Calling it a syndrome may be misleading in the sense that it is a manifestation of increasing intra-synaptic 5-HT levels to which everyone is liable, not an idiosyncratic response like neuroleptic malignant syndrome (NMS). It may be more relevant and helpful to ascertain the symptoms and signs associated with increasing degrees of severity.

The picture in humans is congruent with that seen in animals given drugs that increase intra-synaptic 5-HT. This is characterized by enhanced locomotor activity, forepaw treading, shivering, tremors, hyperexcitability, dilated pupils, salivation, flushing, tachypnoea, hypertension, lateral head weaving, hind limb abduction, arched (straub) tail, pyrexia, myoclonus and seizures (Bogdanski *et al*., 1958; Himwich and Petersen, 1961; Sinclair, 1973; Marley and Wozniak, 1983). There is much imprecision in definitions of SS; the term 'mental status changes' has been used without precise definition. Some features are likely to represent different points on a continuum of severity, e.g. poor concentration > memory impairment > confusion > delirium, or various forms of the same basic phenomenon, e.g. clonus, myoclonus, ocular oscillations, 'oculo-gyric crisis' and eyes deviated upward. One primary element is the hyperactivity which manifests in mental (agitation, hypomania) and physical (restlessness and hyperactivity) forms. The other key features are hyperreflexia, hypertonia/rigidity and particularly clonus (inducible, spontaneous and ocular) (Sternbach, 1991; Hilton *et al*., 1997). The key features of SS and NMS are contrasted in Table 1.

Until the 1980s, it was not generally understood that symptoms were related to excessive intra-synaptic concentrations of 5-HT. This hypothesis had, however, been advanced by a neurologist, Oates, in 1960 following observations of symptoms in patients treated with an MAOI and L-tryptophan (Oates and Sjoerdsma, 1960).

The literature about SS is expanding rapidly; recent reviews summarize the field (Bodner *et al*., 1995; Lejoyeux *et al*., 1995; Mills, 1995; Sporer, 1995; Brown *et al*., 1996; Martin, 1996; Brubacher, 1997; Hilton *et al*., 1997; Lane and Baldwin, 1997). However, few reviews have concentrated on treatment and some of the cases reported here have never been analysed.

Table 1 Serotonin syndrome (SS) versus neuroleptic malignant syndrome (NMS)

Feature	SS	NMS
Serotonin syndrome		
Serotomimetic drug	+ + +	0
Rapid onset	+ + +	0
Mental state changes—agitation	+ + +	Akathisia[a]
Mental state changes—confusion	+	+ +
Mental state changes—hyperactivity	+ + +	0
Clonus	+ + +	0
Myoclonus	+ + +	0
Ocular oscillations	+ + +	0
Shivering	+ + +	0
Tremor	+ + +	+
Hyperreflexia	+ + +	0
Neuroleptic malignant syndrome		
Neuroleptic	0	+ +
Slow onset	0	+ +
Bradykinesia/stupor	0	+ + +
Leaden rigidity	0	+ + +
Autonomic instability	+[b]	+ +
Non-specific		
Hyperpyrexia	+ +	+ +
Diaphoresis	+ +	+ + +
Tachypnoea	+ +	+ + +
Tachycardia	+ +	+ + +
Hypertension	+ +	+ +
Confusion	+ +	+ + +[c]
Raised creatinine phosphokinase	+	+ + +

[a]Akathisia and agitation may be hard to distinguish between. [b]Autonomic instability, may only occur in severe cases. [c]Confusion, probably more severe in NMS.

Methods

Many episodes of SS in the literature, from the late 1950s until the early 1980s, were unrecognized or have been forgotten. The author identified reviews that dealt with 'combined treatment' (TCAs and MAOIs) and studied them for any reports that might represent SS (Ayd, 1961a; Bowen, 1964; Gander, 1965; Schuckit *et al*., 1971; Beaumont, 1973; Sethna, 1974; Ananth and Luchins, 1977; Moller Nielsen, 1980; White and Simpson, 1981; Razani *et al*., 1983; Lieberman *et al*., 1985; Clark and Lipton, 1986; Goldberg and Thornton, 1986). One review considers all drugs which affect body temperature in animals and humans and contains 794 references (Clark and Lipton, 1986). All the drugs mentioned in the present article that have been implicated in SS were cross-checked for human cases which were then checked to see if they met the clinical criteria for SS. An extensive manual search of the literature before the start of the Medline database revealed numerous reports in humans. A total of 12 reports of possible SS were identified before the end of 1962 (Mitchell, 1955; Papp and Benaim, 1958; Palmer, 1960; Shee, 1960; Ayd, 1961b; Babiak, 1961; Brownlee and Williams, 1961; Harrer, 1961; Howarth, 1961; Clement and Benazon, 1962; Cocks and Passmore-Rowe, 1962; Reid, 1962). Computer searches using the terms 'hyperthermia', 'hyperpyrexia', 'serotonin syndrome', or 'toxic' and 'serotonin' and 'MDMA' were carried out and the resultant abstracts scanned. In addition, reports of NMS were examined to ascertain whether cases had been misclassified. The criteria used in this

present paper for assessing whether a case was one of probable SS are in accord with the reports in Table 1.

The degree of seriousness of symptoms (Table 2) has been classified as mild, moderate or severe as an approximate guide for comparison. Mild signifies three definite symptoms from Table 1 but no requirement for action (e.g. treatment or admission to hospital); moderate signifies four or more definite symptoms from Table 1 which between them cause significant impairment of functioning or make medical observation necessary; severe signifies that most symptoms from Table 1 are present or significant impairment of consciousness or functioning is present, to an extent mandating hospital care and active treatment. Further research is required to define more precisely the pattern and progression of symptoms.

Results

Table 2 summarizes the treatment and estimated response of cases given chlorpromazine and cyproheptadine. In chlorpromazine treated cases (a total of 13) seven episodes were severe and of these there was a good response in three and a poor response in four. The poor response, Ciocatto's case, followed a dose of 10 mg of chlorpromazine (Ciocatto *et al*., 1972). Four episodes were rated as being of moderate severity and of these there was a good response in three and moderate response in one. Two cases were rated as mild; these are the previously unreported cases from the present author. They occurred in patients under close observation in a specialist unit and were not unexpected. They were treated at an early stage.

In the cyproheptadine treated cases (a total of seven), none were rated as severe and only three as definite SS. Only three out of the seven were of moderate severity and, of these, one response was good, another was moderate and the third was poor. All three definite cases involved MAOIs, with one response rated as good, a second as moderate and the third (given a high dose of cyproheptadine) as no response at all. Of the total of seven cases, one did not fulfil criteria for SS and one should be regarded as a 'possible', leaving only five as probable or definite. Three of these five either had no or a poor response. In only one case was the response rated as good. The improvement, within 30 min of only 4 mg of cyproheptadine, is rapid for oral onset of action and may represent spontaneous resolution.

Discussion

There is great difficulty in assessing response in such cases where the natural course of the reaction is not known with certainty. The varied nature and circumstances of these reports prevents much useful comparison with other cases not treated with chlorpromazine or cyproheptadine. All the severe cases occurred with MAOIs. The definite cases treated with cyproheptadine were of moderate severity and show little indication of improvement, only one was rated as a moderately good response. In the chlorpromazine cases, there is a stronger suggestion of response; in the seven severe cases, three out of seven showed good response. In the four moderately severe cases, three out of four showed good responses and one a moderate response. It is salutary to note from recent reports how rapid (within 2 h) patients' deterioration can be (George and Godleski, 1996; Mathew *et al*., 1996; Robert *et al*., 1996), especially with combinations such as CMI and tranylcypromine (TCP) (Corkeron, 1995; Brubacher *et al*., 1996; Gillman, 1996). Both rapidity of onset and severity of symptoms are related to high potency drugs, larger doses and the route of administration (IV > IM > oral). The duration of the reaction will have some relationship to the elimination half-life which is long with CMI and fluoxetine (Pato *et al*., 1991; Coplan and Gorman, 1993). The old MAOIs bind irreversibly with MAO which may take 2 weeks or more to return to normal levels (Arnett *et al*., 1987). SS has been reported up to 4 weeks after ceasing a selective irreversible MAOI (clorgyline) (Insel *et al*., 1982). The largest series of fatal reactions documented (seven deaths) was with MAOIs given after fluoxetine (Beasley *et al*., 1993). In these cases, TCP was started between 12 h (case 1), and a few days, after fluoxetine. These reports illustrate that a thorough knowledge of the potency, pharmacodynamics and pharmacokinetics of drugs is needed to judge the likelihood of reactions in individual cases.

Small changes of dosage of some drugs may markedly increase effects and there is evidence of a fine line between side-effects and toxicity; this was evident in several of the author's cases, especially those involving TCP. Symptoms only developed after the dose had been increased from 20–30 mg per day. This accords with the author's clinical impression from treating many patients with TCP which is that few get an optimal improvement with less than 30 mg per day. One unusual paper reports the side-effects encountered in 45 cases where CMI and TCP were administered together (Oefele *et al*., 1986). Treatment was ceased because a 'toxic delirium' occurred in three cases, 'instable (sic) blood pressure, sweating and tremor' in four other cases and in a further three 'gross tremor and hyperthermia'. Although the 22% incidence of severe side-effects mandating cessation of treatment is high, it is noteworthy that there was no mortality in this series. This may be attributable to the low maximum dose of only 20 mg of TCP.

Serotonin syndrome and neuroleptic malignant syndrome: differential diagnosis

The differential diagnosis between SS and NMS (see Table 1) has caused difficulties in a few reported cases (Brennan *et al*., 1988; Kline *et al*., 1989; Staufenberg and Tantum, 1989; Stern *et al*., 1992; Ames and Wirshing, 1993; Graber *et al*., 1994). These difficulties have arisen partly because some patients were taking neuroleptics, which seems to have influenced the exclusion of a diagnosis of SS. A presumptive diagnosis of NMS was thus made when the clinical picture indicated SS. In one patient (already on regular chlorpromazine), the dose of chlorpromazine had just been reduced before symptoms developed and it is possible that the protective effect of 5-HT receptor blockade, thus lessened, allowed symptoms to emerge (Staufenberg and Tantum, 1989).

Table 2 Drug treatment of serotonin syndrome

Author	Seroto-mimetic drugs	Rapid onset	Shivering	Tremor	Hyper-active/ agitated	Confusion	Clonus	Myoclonus	Ocular oscillations	Hyper-reflexia	Diaphor-esis	Hyper-pyrexia	Diarrhoea	Ataxia	SS diagnosis	Symptom severity	Dose of CPZ	Comments	Response
Papp	iproniazid 150 mg daily and meperidine 200 mg IMI	+ + +		+ + +	+ + +	+ + +	+ + +								Definite	Severe	50 mg IM	Responded in 30 min	Good
Clement	iproniazid and meper-idine 20 mg IV	+ + +			+ + +					+ +	+ + +	+ + + (40 °C)			Probable	Severe	50 mg IV	Responded in 20 min	Good
Grantham	IMI 100 mg daily, ceased, next day TCP 30 mg	After 6 days on TCP			+ +	+ +	+ + +			+ + +	+ + +	+ + (39.4 °C)			Definite	Severe	50 mg IM	Severely ill for 24 h. Improve-ment 1 h after CPZ	Good
Ciacotto	OD of IMI and TCP (unknown quantity)	+			+ + +	+ + +		+ + +				+ + + (42 °C)			Definite	Severe	10 mg IV	Overdose	Poor
Robertson	OD IMI and TCP	+			+ +	+		+ + +			+ +	+ + (41 °C)			Probable	Severe	100 mg IM	Improved after a further 70 mg CPZ IV	Moderate
Graham	phenelzine 60 mg daily and one dose IMI 150 mg	+ + +	+ + +		+ +	+ + +				+ +		+ 37.8 °C)			Definite	Moderate	50 mg IM		Good
Tackley	TCP and CMI 10 mg twice daily (concur-rently)	+ + +	+ + +		+ + +	+ +					+ +	+ + + (42.9 °C)	+ +	+ + +	Definite	Severe	50 mg IM	Died	Poor
Brodribb, 1995	moclobe-mide 300 mg daily and imipramine 200 mg daily	0	+ +			+ +		+ +	+			+ + (39.6 °C)		+	Probable	Severe	200 mg IM	IMI level 1518 µg/l	Poor
Gillman, 1996	CMI 100 mg ceased 13 days later TCP 30 mg	+ +	+ + +		+ + +	+		+ +			+				Definite	Moderate	100 mg IM	No re-sponse to cyproheptadine 16 mg	Good
Gillman, 1997	OD CMI 17 days la-ter on TCP 30 mg	+ + +	+ + +	+ +	+ + +	+		+ +			+ +				Definite	Moderate	50 mg IM	Same pa-tient—2 episodes	Moderate
Gillman, 1997	TCP 40 mg OD CMI plasma le-vel 150 µg/l	+ +	+ + +	+ +	+ + +	+		+ + +							Definite	Moderate	150 mg IM		Good
Gillman*	sertraline 200 mg—ceased 13 days later TCP 30 mg	+ +	+ +	+ + +	+ +			+ +							Definite	Mild	50 mg oral	In hospi-tal—early interven-tion	Good

(continued)

Table 2 *(continued)*

Author	Serotonin-mimetic drugs	Rapid onset	Shivering	Tremor	Hyperactive/agitated	Confusion	Clonus	Myoclonus	Ocular oscillations	Hyperreflexia	Diaphoresis	Hyperpyrexia	Diarrhoea	Ataxia	SS diagnosis	Symptom severity	Dose of CPZ	Comments	Response
Gillman*	sertraline 100 mg—ceased 13 daya later TCP 30 mg	+ +	+ +			+	+ +	+ +		+ +					Definite	Mild	50 mg oral	In hospital—early intervention	Moderate

Author	Serotonin-mimetic drugs	Rapid onset	Shivering	Tremor	Hyperactive/agitated	Confusion	Clonus	Myoclonus	Ocular oscillations	Hyperreflexia	Diaphoresis	Hyperpyrexia	Diarrhoea	Ataxia	SS diagnosis	Symptom severity	Dose of CYP	Comments	Response
Goldberg	trazadone and buspirone	0	0	0	0		0	+ +	0	0	0	0			Not SS	Mild	12 mg	Only symptom was myoclonus	Moderate
Muly	fluoxetine 40 mg and lithium 300 BD	+	+ +	+ +	+ +		+ +	+ +		+ +		0			Definite	Mild	12 mg (time unstated)	LI ceased; improved over 4 days	Poor
Beasley	fluoxetine 20 mg ceased; 7 days later TCP 40 mg	+ +				+ +			+ +					+ +	Possible	Mild	16 mg	Few details given	Moderate
Lappin	isocarboxazid ceased; 11 days later sertraline 100 mg × 1 only	+ + +			+ +			+ +			+ +	0			Definite	Moderate	Two doses of 4 mg (in 1 hr)	Propranolol 1 mg (IV) gave no response	Moderate
Klysner	isocarboxazid 30 mg daily; venlafaxine 75 mg added	+ +	+ +		+ + +			+ +		+ +	+ +				Definite	Moderate	4 mg 6 hourly for 'days'	Symptoms reduced over 6 days	Poor
George	fluoxetine 20 mg and trazodone 100 mg	0	+ +	+ +	+ +		0	+ +		+ +	+ +				Probable	Moderate	4 mg once only	Responded within 30 min	Good
Gillman, 1996	CMI and TCP	+ + +	+ + +	+ +	+ + +	+		+ +			+ +				Definite	Moderate	16 mg	Subsequently responded to CPZ	None

CMI, clomipramine; CPZ, chlorpromazine; CYP, cyproheptadine; IMI, imipramine; SS, serotonin syndrome; TCP, tranylcypromine. 0, not present; +, mild; + +, moderate; + + +, severe. Blank space indicates a feature was not mentioned or cannot be inferred from the report.

Features differentiating between SS and NMS (Rosebush and Stewart, 1989; Rosenberg and Green, 1989; Caroff and Mann, 1993; Persing, 1994) may be: NMS, slow onset (days to weeks) and slow progression over 24–72 h in association with neuroleptics versus SS, both rapid onset and rapid progression (minutes to hours) in association with a combination of serotonergic drugs; NMS, bradykinesia and lead pipe rigidity versus SS, hyperkinesia and clonus; and NMS, an idiosyncratic reaction to therapeutic dosages versus SS, a manifestation of toxicity (usually to a combination of drugs) to which everyone is liable.

In summary, the precipitating drug defines the syndrome: dopamine (DA) receptor blockers produce bradykinesia whereas serotonergic drugs produce hyperkinesia.

Treatment

Many treatments for SS have been described including the 5-HT_2 blockers, methysergide (Sandyk, 1986) and cyproheptadine (see Table 2) (Goldberg and Huk, 1992; Beasley *et al*., 1993; Muly *et al*., 1993; Lappin and Auchincloss, 1994; Klysner *et al*., 1995; George and Godleski, 1996), and the 5-HT_{1A} blocker propranolol (Rivers and Horner, 1970; Guze and Baxter, 1986; Klee and Kronig, 1993; Lappin and Auchincloss, 1994; Ruiz, 1994; Heisler *et al*., 1996; Gillman, 1997b). Various benzodiazepines have been used (Halman and Goldblum, 1990; Ooi, 1991; Lejoyeux *et al*., 1992; Nierenberg and Semprebon, 1993; Brannan *et al*., 1994; Graber *et al*., 1994; Ruiz, 1994; Skop *et al*., 1994; Baetz and Malcolm, 1995; Reeves and Bullen, 1995; Hodgman *et al*., 1997) as well as nitroglycerine (Brown and Skop, 1996), and chlormethiazole (Bedford-Russel *et al*., 1992). Neuroleptics have been used, mostly chlorpromazine as reviewed herein (see Table 2), but also chlorprothixene (Morch, 1962) and haloperidol, unsuccessfully (Bedford-Russel *et al*., 1992).

The relative potency for blockade of 5-HT_{2A} receptors by various drugs is given in Table 3 (Wander *et al*., 1987; Richelson, 1996; Richelson *et al*., 1997). Chlorprothixene and sertindole are the most potent blockers closely followed by risperidone. Chlorpromazine and cyproheptadine are of similar, but lesser, potency and haloperidol has a low affinity. All these drugs show affinities at 5-HT_{1A} receptors two to three orders of magnitude less (Wander *et al*., 1987). This author's initial use of chlorpromazine for SS (Gillman, 1997b) was prompted following the failure of 16 mg of cyproheptadine (orally), which was the biggest dose then reported (Goldberg and Huk, 1992; Beasley *et al*., 1993; Lappin and Auchincloss, 1994). The receptor affinity data (see Table 3) accords well with the limited clinical experience in these reports, i.e. the successful use of chlorpromazine, chlorprothixene and cyproheptadine and the apparent failure of haloperidol (Bedford-Russel *et al*., 1992).

There seems to be concern that chlorpromazine would aggravate seizures by lowering the seizure threshold. Little has been cited to support this and none of the work reviewed here contains evidence for this. Espelin used chlorpromazine to treat hyperpyrexia following amphetamine intoxication, which presents a similar picture, and specifically stated that it helped to normalize the electroencephalogram (Espelin and Done, 1968). Green also noted there was concern that neuroleptics caused NMS and could aggravate hyperthermia by lowering DA (Green *et al*., 1995). However, the hyperthermia of NMS is an idiosyncratic response to neuroleptics; the normal response is hypothermia. Indeed there is evidence that normal DA activity is needed for the expression of SS (Green and Grahame-Smith, 1974), thus lowering DA may help to ameliorate it (Marley and Wozniak, 1985). Chlorpromazine might cause problems by lowering the blood pressure and would be expected to worsen the clinical state if NMS is confused with SS; it should also be noted that bromocriptine, which has frequently been used to treat NMS, has been reported to increase brain 5-HT levels (Snider *et al*., 1975) with the attendant risk that this could worsen SS (Gillman, 1997a) when it is confused with NMS. An example of such a case may be that of Kline *et al*. (1989) where treatment with dantrolene and bromocryptine was given to a patient with SS and the temperature then rose from 38.1 °C to 42.2 °C within 3 h and death ensued.

Table 3 Blockade of 5-HT_{2A} receptors by various drugs

Drug	5-HT_{2A} affinity
Cyproheptadine	100
Chlorpromazine	71
Chlorprothixene	233
Haloperidol	2.8
Clozapine	62
Risperidone	170
Olanzapine	25
Sertindole	260
Methysergide	14
Ketanserin	178

Affinity $= 10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation in molarity.
Adapted from Wander *et al*. (1987), Richelson (1996), Richelson *et al*. (1997).

When considering whether drug treatment is required it should be noted the earliest studies indicated that in animal models barbiturate anaesthesia and paralysis reduced body temperature (Himwich, 1962). An example of the successful use of anaesthesia, paralysis and active cooling is the report of Peebles-Brown (Peebles-Brown, 1985). A recent review of rapid cooling techniques is that of Harker and Gibson (1995). However, hyperactivity is not the main cause of hyperthermia (Green *et al*., 1995) so these measures alone may not be sufficient.

Analysis of the cases in this review suggests a reasonable starting dose for treatment with chlorpromazine would be 50 mg by IM injection. Larger doses were used in some cases (150 mg by IM injection over 2 h). In Brodribb's case (Brodribb *et al*., 1994), 100 mg by IM injection was given twice in 6 h with a further five doses of 100 mg every 6 h (orally) until discharge (Brodribb, personal communication). In severe cases it is probably reasonable to use an initial dosage of 50–100 mg by IM injection. Cyproheptadine is only available in tablet form. It can be crushed and given via a naso-gastric tube. Doses of 4–16 mg, used in reported cases, may be too low for optimum benefit; Kapur's recent data using

positron emission tomography indicate that about 30 mg is needed (as a single oral dose) to achieve 85–95% blockade of brain 5-HT_{2A} receptors (Kapur *et al*., 1997). This is supported by one of this author's cases where 16 mg of cyproheptadine failed to provide any amelioration of symptoms in a moderately severe case, whereas chlorpromazine 50 mg IM was followed by resolution of symptoms in 2 h (Gillman, 1997b). The evidence for the clinical effectiveness of chlorpromazine and cyproheptadine in human cases of SS is somewhat unsatisfactory because it is based on post hoc analysis of case reports. However, it is supported by extensive data from animal work that clarifies the role of 5-HT. More work is needed, especially to elucidate the extent to which various combinations of drugs raise intra-synaptic 5-HT, which is probably the most important factor determining severity.

Rapid deterioration over 2–4 h is well documented in many recent reports (Beasley *et al*., 1993; Brodribb *et al*., 1994; Graber *et al*., 1994; Corkeron, 1995; Brubacher *et al*., 1996; George and Godleski, 1996; Gillman, 1996; Mathew *et al*., 1996) which suggests a conservative approach to treatment may not always be justified, especially when potent and long acting drugs are implicated, e.g. non-specific MAOIs (TCP and phenelzine) with serotonin reuptake inhibitors like CMI and fluoxetine. Even RIMAs like MOC (in overdose) have been involved in cases exhibiting rapid deterioration or death (Brodribb *et al*., 1994; Hernandez *et al*., 1995; Kuisma, 1995; Power *et al*., 1995; Francois *et al*., 1997).

Conclusions

SS is a potentially serious condition that can worsen rapidly. Paralysis and active cooling may not be sufficient treatment in severe cases; these may require 5-HT_2 blocking drugs as a life saving measure. The evidence suggests that cyproheptadine and chlorpromazine may be effective. In milder cases, these drugs can provide relief of distressing symptoms. Consideration of the factors discussed in this review may aid in balancing the risks and benefits of active intervention with drugs. Where the diagnosis is uncertain, and NMS is a possibility, it may be advisable to avoid both bromocriptine and chlorpromazine. In such cases, paralysis and rapid cooling, and/or cyproheptadine, may prevent the development of disseminated intravascular coagulation and other complications, which can be fatal.

Note: Since the final draft was accepted (January 1998) and publication (March 1999) there have been six further papers reporting the use of cyproheptadine for SS describing a total of 18 further cases. These reports do not alter the views or conclusions expressed in the present paper. [See also Gillman PK (1998) Serotonin syndrome: history and risk. Fund Clin Pharmacol *12*: 482–491.]

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