Medicines Adverse Reactions Committee

Meeting date	13 June 2019	Agenda item	3.2.4
Title	**Sertraline and Nortriptyline: Potential Drug-Drug Interaction**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**		**Sponsor**
Sertraline	*Arrow-Sertraline* Film coated tablets (50mg and 100mg)		Teva Pharma (New Zealand) Limited
	Zoloft Film coated tablets (50mg, 100mg, and 200mg)		Pfizer New Zealand Limited
	Setrona Film coated tablets (50mg and 100mg)		Douglas Pharmaceuticals Limited
Nortriptyline	*Norpress* Tablets (10mg and 25mg)		Mylan New Zealand Limited
PHARMAC funding	Sertraline: *Arrow–Sertraline* Film coated tablets (50mg and 100mg): Fully subsidised Nortriptyline: *Norpress* tablets (10mg and 25mg): Fully subsidised		
Previous MARC meetings	This topic has not been discussed by the MARC to date.		
Prescriber Update	• Watching Briefs: SSRI/TCA Interactions and Serotonin syndrome – June 2006 www.medsafe.govt.nz/profs/PUArticles/watchingbriefsJune06.htm#SSRI2 • Serotonin Syndrome/Toxicity Reminder – December 2010 www.medsafe.govt.nz/profs/PUArticles/SerotoninSyndromeToxicityReminder.htm • Serotonin Syndrome: Short Time to Onset, Even with the First Dose – March 2016 www.medsafe.govt.nz/profs/PUArticles/March2016/SerotoninSyndrome.htm		
Classification	Prescription medicine		
Usage data	DataPharm (beta) shows the following usage data for 2018 (the most recent year for which data is available). The data shows the number of people who received a dispensing in 2018. The data presented are limited to medicines which are funded by PHARMAC and dispensed from a community pharmacy.		
Advice sought	**The Committee is asked to advise:** • Whether the presented evidence is sufficient to warrant updates to the sertraline and nortriptyline data sheets. If so how should they be updated? • Whether there is need for further communication of this issue outside of MARC's Remarks in *Prescriber Update*.		

Medicine	**Number of Patients**
Sertraline 50mg tablets	48719
Sertraline 100mg tablets	17365
Nortriptyline 10mg tablets	52643
Nortriptyline 25mg tablets	20292

Table of Contents

1 PURPOSE

Medsafe reviewed an adverse drug reaction (ADR) report (ID: 125559) submitted to the Centre for Adverse Reactions Monitoring (CARM) as part of routine pharmacovigilance. The report described a suspected drug-drug interaction between sertraline and nortriptyline. It was noted that there is currently no wording in the data sheets specifically describing a drug-drug interaction between nortriptyline and sertraline. As a result, Medsafe investigated the literature for evidence of such an interaction.

The advice sought from the Committee is whether the presented evidence is sufficient to warrant inclusion of information regarding a drug-drug interaction in both the sertraline and nortriptyline data sheets.

2 BACKGROUND

2.1 CARM case report 125559 (annex 1)

[redacted]

2.2 Serotonin syndrome

2.2.1 Introduction

Serotonin syndrome is a drug induced syndrome characterised by a cluster of dose related adverse effects that are due to increased serotonin concentrations in the central nervous system (CNS). It is also known as serotonin toxicity as it covers a spectrum from mild through to severe adverse effects depending, presumably, on the extent of increased serotonin (1).

Severe serotonin toxicity usually occurs only with a combination of two or more serotonergic medicines (even when each is at a therapeutic dose), one of which is generally a monoamine oxidase inhibitor (MAOI). Moderate toxicity has been reported with an overdose of a single medicine and occasionally from increasing therapeutic doses (1).

A list of medicines that have been associated with moderate to severe serotonin toxicity is provided below in Table 1.

Table 1: Medicines that have been associated with moderate to severe serotonin toxicity (1)

Monoamine oxidase inhibitors

- Irreversible inhibitors—Phenelzine, tranylcypromine, iproniazid, isocarboxazid
- Reversible inhibitors of monoamine oxidase A—Moclobemide
- Non-psychotropic drugs—Linezolid, methylene blue (methylthioninium chloride)

Serotonin releasing agents

- Fenfluramine, sibutramine
- Amphetamine, methamphetamine, methylphenidate, phentermine
- Synthetic stimulants—Ecstasy, "bath salts" (cathinones, phenylethylamines)
- Serotonin reuptake inhibitors
- Selective serotonin reuptake inhibitors—Fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, escitalopram
- Serotonin-noradrenaline reuptake inhibitors—Venlafaxine, desvenlafaxine, duloxetine
- Tricyclic antidepressants—Clomipramine, imipramine
- Opioid analgesics—Pethidine, tramadol, fentanyl, dextromethorphan
- St John's wort (*Hypericum perforatum*)

Miscellaneous

- Lithium
- Tryptophan
- Buspirone

*Severe serotonin toxicity generally involves a combination of agents from different drug classes[3 4 8-12]

Comment: Sertraline is listed in the table, however nortriptyline is not. Other tricyclic antidepressants (TCAs) including clomipramine and imipramine are listed. The authors state that clomipramine and imipramine are much more serotonergic than other tricyclic antidepressants and have caused serotonin toxicity (1).

2.2.2 Signs and symptoms

Serotonin toxicity starts within hours of ingesting medicine(s) that cause an increase in serotonin (1).

The classic triad of clinical features are neuromuscular excitation (e.g. clonus, hyperreflexia, myoclonus, and rigidity), autonomic nervous system excitation (e.g. hyperthermia and tachycardia) and altered mental state (e.g. agitation and confusion) (1).

Patients with mild cases may be afebrile but have tachycardia, with a physical examination that is notable for autonomic findings such as shivering, diaphoresis (sweating), or mydriasis. The neurological examination may reveal intermittent tremor or myoclonus, as well as hyperreflexia (2). Mild serotonin syndrome can be difficult to distinguish from many medical conditions or other adverse effects (1).

A representative example of a moderate case involves such vital-sign abnormalities as tachycardia, hypertension, and hyperthermia core temperature as high as 40°C is common in moderate intoxication. Common features of the physical examination are mydriasis, hyperactive bowel sounds, diaphoresis, and normal skin colour. The hyperreflexia and clonus seen in moderate cases may be considerably greater in the lower extremities. Patients may exhibit horizontal ocular clonus. Changes in mental state include mild agitation or hypervigilance, as well as slightly pressured speech (2).

A patient with a severe case of serotonin syndrome may have severe hypertension and tachycardia that may abruptly deteriorate into frank shock. Such patients may have agitated delirium as well as muscular rigidity and hypertonicity. As with moderate cases, the increase in muscle tone is considerably greater in the lower extremities. The muscle hyperactivity may produce a core temperature of more than 41.1°C in life-threatening cases (2).

The spectrum of clinical features of serotonin syndrome is shown below in Figure 1.

Additionally, the Hunter serotonin toxicity criteria, which can assist in the diagnosis of moderate or severe serotonin toxicity is presented below in Figure 2.

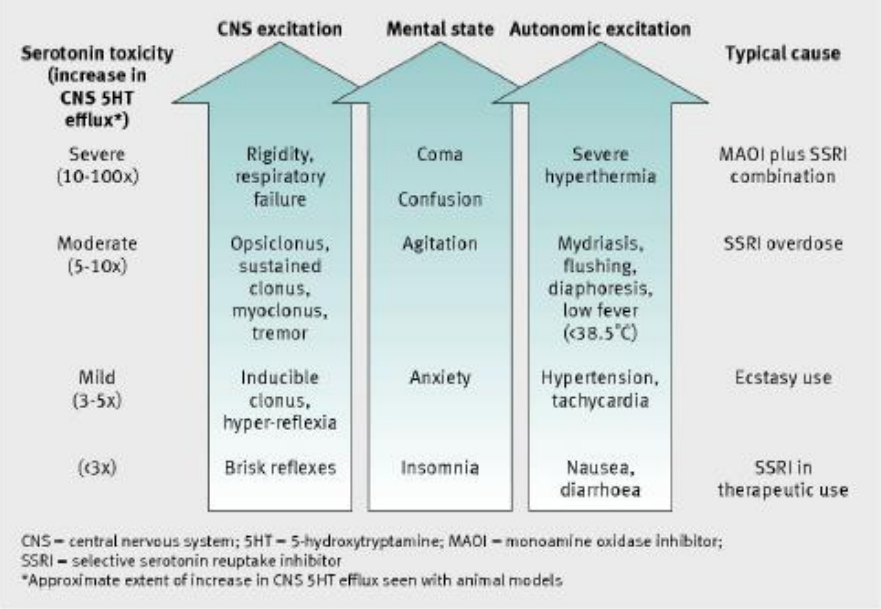


Figure 1: Spectrum of effects according to the triad of common clinical features in serotonin syndrome (1)

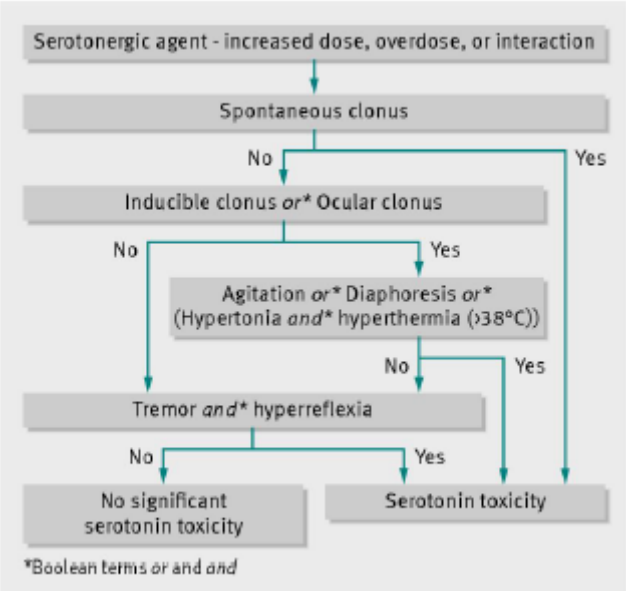


Figure 2: The Hunter serotonin toxicity criteria flowchart (1)

Comment: There are distinguishable differences between serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS). NMS is an idiopathic reaction to dopamine antagonists, a condition that is defined by a slow onset, bradykinesia or akinesia, "lead pipe" muscular rigidity, hyperthermia, fluctuating consciousness, and autonomic instability. Signs and symptoms of NMS typically evolve during several days, in contrast to the rapid onset and hyperkinesia of the serotonin syndrome (2).

2.2.3 Pathophysiology of serotonin syndrome

No single receptor appears to be responsible for the development of serotonin syndrome, although several sources of evidence suggest that agonism of 5-HT_{2A} receptors contributes substantially to the condition. Additional subtypes of serotonin receptors, such as 5-HT_{1A}, may contribute through a pharmacodynamic interaction in which increased synaptic concentrations of serotonin saturate all receptor subtypes (2).

Noradrenergic central nervous system (CNS) hyperactivity may play a critical role, since the degree to which CNS norepinephrine concentrations are increased in serotonin syndrome may correlate with the clinical outcome (2).

Other neurotransmitters, including NMDA receptor agonists and GABA may affect the development of the syndrome but the role of these agents is less clear (2).

The addition of medicines that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has been associated with the condition (2).

2.2.4 Relevant information on serotonin syndrome currently in the data sheets

2.2.4.1 Sertraline (Arrow-Sertraline, Zoloft, Setrona)

4.4 Special warnings and precautions for use

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)

The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported with SSRIs, including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic drugs (including triptans and fentanyl), with drugs which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Some signs of SS, including

hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes resemble NMS. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see Section 4.3 Contraindications).

Other Serotonergic Drugs

Co-administration of sertraline with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan, fenfluramine, fentanyl and its analogues, tramadol, 5-HT agonists, dextromethorphan, pethidine or methadone should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction.

4.8 Undesirable effects

Nervous System Disorders: Coma, convulsions, cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome), headache, migraine, movement disorders (including extrapyramidal symptoms such as dyskinesia, akathisia, dystonia, hyperkinesia, hypertonia, teeth grinding or gait abnormalities), muscle contractions involuntary, paraesthesia, hypoaesthesia, dysgeusia, speech disorder, disturbance in attention, amnesia and syncope. Also reported were signs and symptoms associated with serotonin syndrome: in some cases associated with concomitant use of serotonergic drugs, these included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia.

Comment: Contains relevant information regarding serotonin syndrome, but does not consider nortriptyline (or any other tricyclic antidepressant) to be a serotonergic drug(s).

2.2.4.2 Nortriptyline (Norpress)

There is currently no information on serotonin syndrome in the data sheet (3).

2.3 Indications and pharmacodynamic/pharmacokinetic properties

2.3.1 Sertraline

2.3.1.1 Indications

Sertraline is a selective serotonin reuptake inhibitor (SSRI) approved in New Zealand for the treatment of:

Children and Adolescents (6-17 years)

- Obsessive compulsive disorder (OCD)

Adults

- Symptoms of depression, including depression accompanied by symptoms of anxiety, in patients with or without a history of mania
- Obsessive compulsive disorder (OCD)
- Panic disorder, with or without agoraphobia
- Post-traumatic stress disorder (PTSD)
- Social phobia (social anxiety disorder)
- Premenstrual dysphoric disorder (4)

2.3.1.2 Pharmacodynamic properties

Sertraline is a potent and selective inhibitor of presynaptic neuronal serotonin (5-HT) reuptake, which results in the potentiation of the effects of 5-HT. It has only very weak effects on noradrenaline and dopamine neuronal reuptake (4).

Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors (4).

2.3.1.3 Pharmacokinetic properties

At least five isoforms of CYP (2B6, 2C9, 2C19, 2D6 and 3A4) are involved in the metabolism of sertraline, but since the contribution of any individual isoform does not exceed 40% of the overall metabolism, concurrent administration of a drug that inhibits one of these isoforms is unlikely to cause a marked increase in the plasma concentration of sertraline (5).

The plasma elimination half-life of sertraline is about 26 hours, which allows for once daily dosing. N-desmethylsertraline, the major metabolite, has a plasma half–life of about 62 to 104 h. The metabolite appears to lack serotonin reuptake inhibiting properties in *in vitro* and *in vivo* studies (5).

Sertraline mildly inhibits the CYP2D6 isoenzyme. Sertraline's effect on CYP1A2, CYP3A3/4, CYP2C9, and CYP2C19 appears minimal (5). Studies have reported that the co-administration of sertraline with TCAs can increase the plasma concentrations of desipramine, imipramine and nortriptyline (5, 6).

Sertraline is highly plasma protein bound (~98%) and may interact with other highly protein bound drugs (5, 7).

2.3.2 Nortriptyline

2.3.2.1 Indications

Nortriptyline is a tricyclic antidepressant (TCA) approved in New Zealand for the:

- relief of symptoms of depression
- treatment of nicotine dependence as an aid to smoking cessation (3)

2.3.2.2 Pharmacodynamic properties

Tricyclic antidepressants inhibit reuptake of both serotonin and norepinephrine, which increases the amount of neurotransmitter in the synaptic cleft. These effects are thought to mediate the therapeutic benefit of cyclic antidepressants (8).

Tricyclics are subdivided into two categories:

- Tertiary amines (e.g. amitriptyline, clomipramine, doxepin, imipramine, and trimipramine). These are generally more potent in blocking reuptake of serotonin compared with norepinephrine.
- Secondary amines (e.g. desipramine, nortriptyline, and protriptyline). Secondary amines are more potent in blocking reuptake of norepinephrine than serotonin (8).

Nortriptyline is similar to desipramine in that they both block reuptake of norepinephrine and serotonin, but more potently block reuptake of norepinephrine. Its antidepressant effect is thought to be due to blocking reuptake of norepinephrine and serotonin (8).

This appears to agree with data from human cloned receptor experiments, as shown in Table 2 (9).

Table 2: Receptor profile K_i (nmol/L) of TCAs and comparator drugs: uptake inhibition and receptor antagonism (HCR data) (9)

Drug	*Reuptake inhibition*		*Post-synaptic receptor antagonism*			
	5-HT	*NA*	*H1*	α_1	*Musc*	*5-HT$_{2A}$*
Mirtazapine*	>10 000	4600	0.14	500	670	16
Mianserin*	>4000	71	0.40	34	820	7
Doxepin	68	29.5	0.24	24	83	25
Amitriptyline	20	50	1	27	18	29
Imipramine	7	60	40	32	46	80
Clomipramine	0.14	54	15	32	25	35
Nortriptyline	100	10	6.3	55	37	44
Dothiepin	78	70	4	400	38	260
Desipramine*	18	0.83	110	100	100	280
Reboxetine*	58	7.2	310	>1000	>1000	>1000

Abbreviations: HCR, human cloned receptor.
Smaller K_i values represent greater potency. Note: where values are available from different laboratories and different experiments, affinities can vary by about one order of magnitude; mid-range values are given (Table 2a and b gives ranges).
Receptors: H1, Histamine type 1; Musc, acetylcholine muscarinic; α_1, α_1 adrenoceptor. Note that no HCR data are known for lofepramine.
All data have been extracted from PDSP K_i database, http://pdsp.med.unc.edu/pdsp.php (except *Richelson, 2001).

Comment: UpToDate suggests that nortriptyline has some effect on inhibiting serotonin reuptake, but is more potent for noradrenaline/norepinephrine reuptake inhibition.

The British Journal of Pharmacology article suggests that nortriptyline has some potency for inhibiting 5-HT reuptake, according to experiments using human cloned receptors, but more so for noradrenaline/norepinephrine. Also appears to have some inhibitory effect on 5-HT$_{2A}$ according to this data. The 5-HT$_{2A}$ receptor is thought to contribute substantially to developing serotonin syndrome (see section 2.2.3).

2.3.2.3 Pharmacokinetic properties

Nortriptyline is the active, demethylated metabolite of amitriptyline (8). It is stated to be a substrate of the following CYP450 enzymes: CYP2D6 (major), CYP1A2 (minor), CYP2C19 (minor), CYP3A4 (minor) (10).

The elimination half-life in adults is reported to be 14 to 51 hours (mean: 26 hours) and for the elderly, 23.5 to 79 hours (mean 45 hours) (10).

All tricyclic antidepressants bind strongly to plasma albumin (90-95%) at therapeutic plasma concentrations (9).

Nortriptyline (and desipramine) are the least problematic of the tricyclic antidepressants in terms of drug interactions, being only weak CYP450 2D6 inhibitors. They are unlikely to be involved in clinically relevant interactions unless the serum levels are high, for example following overdose, or in poor metabolisers (9).

Table 3: Degree of CYP450 enzyme inhibition of antidepressants at their usual therapeutic dose (9)

Drug	*Cytochrome P450 enzyme inhibition*				
	2D6	*1A2*	*3A4*	*2C9*	*2C19*
Nortriptyline	+	0	0	0	+
Desipramine	+	0	0	0	+
Amitriptyline	+	++	0	+	+++
Imipramine	+	++	+	+	+++
Dothiepin	+	+?	0?	+?	+++?
Doxepin	+	+?	0?	+?	+++?
Clomipramine	+?	++?	0	+?	+++
Sertraline	+	0	0	0	0
Fluoxetine	+++	0	+	++	+++
Fluvoxamine	+	+++	++	+++	+++
Paroxetine	+++	0	0	0	0
Citalopram	++	0	0	0	0
Escitalopram	++	0	0	0	0
Venlafaxine	+	0	0	0	0
Duloxetine	++	0	0	0	0

Guide to approximate ranking of effect.
+=measurable, but likely to be clinically insignificant.
++=clinically significant, possibly serious with other drugs with narrow safety margins.
+++=large, often clinically significant, serious interactions highly predictable with certain drugs.
'?' indicates an estimate from structurally related drugs, because there are no data available for that specific drug.
No data known for lofepramine.

Comment: Sertraline and nortriptyline are both listed as weak inhibitors of CYP2D6. This enzyme appears to play a role in the metabolism of both medicines. Nortriptyline is also listed as a weak CYP2C19 inhibitor, too.

According to this table, other SSRIs appear to have a greater inhibitory effect on CYP2D6 than sertraline.

2.4 Other drug-drug interaction information in the data sheets

Current data sheet information that implies a possible drug-drug interaction between sertraline/SSRIs and nortriptyline/tricyclic antidepressants includes:

2.4.1 Sertraline

2.4.1.1 Arrow-Sertraline, Zoloft, Setrona

4.4 Special warnings and precautions for use

Abnormal Bleeding/Haemorrhage

Bleeding abnormalities have been reported with the use of SSRIs (including purpura, haematoma, epistaxis, vaginal bleeding, ecchymoses, gastrointestinal bleeding and life-threatening haemorrhage). This risk may be potentiated by concurrent use of atypical antipsychotics and phenothiazines, most tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or other medicines that affect coagulation. Sertraline should therefore be used with caution in patients concomitantly treated with medicines that increase the risk of bleeding or in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

4.5 Interaction with other medicines and other forms of interaction

Drugs Metabolised by Cytochrome P450 (CYP) 2D6

There is variability among antidepressants in the extent to which they inhibit the activity of isozyme cytochrome CYP 2D6. The clinical significance of this depends on the extent of the inhibition and the therapeutic index of the co-administered drug. CYP 2D6 substrates with a narrow therapeutic index include TCAs and class 1C antiarrhythmics such as propafenone and flecainide. In formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation (mean 23-37%) of steady state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity).

Comment: Suggests that concomitant use of TCAs and SSRIs can result in an increased risk of bleeding.

Additionally, it states that sertraline has shown some potential to mildly increase plasma levels of TCAs metabolised by CYP2D6, including the secondary amine TCA desipramine.

Nothing explicitly stated about nortriptyline.

2.4.2 Nortriptyline

2.4.2.1 Norpress (3)

4.4 Special warnings and precautions for use

There is a warning for patients with a history of seizures. It states that nortriptyline can lower the seizure/convulsive threshold. It also states that generally nortriptyline must not be used for smoking cessation (unless there is compelling clinical justification) in patients who have predisposing risk factors, including concomitant use of medicines known to lower seizure threshold, such as antidepressants.

4.5 Interaction with other medicines and other forms of interaction

There is information regarding the use of medicines metabolised by CYP2D6 (P450 IID6), including SSRIs.

Medicines metabolised by P450IID6

A subset (3% to 10%) of the population has reduced activity of certain medicine metabolising enzymes such as the cytochrome P450 isoenzyme P450IID6. Such individuals are referred to as "poor metabolisers" of medicines such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. These individuals may have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses. In addition, certain medicines that are metabolised by this isoenzyme, including many antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isoenzyme, and thus may make normal metabolisers resemble poor metabolisers with regard to concomitant therapy with other medicines metabolised by this enzyme system, leading to medicine interactions.

Concomitant use of tricyclic antidepressants with other medicines metabolised by cytochrome P450IID6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other medicine. Therefore, co-administration of tricyclic antidepressants with other medicines that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

Comment: Implies that concomitant use of nortriptyline and antidepressants can reduce seizure threshold. Recommends avoiding in patients with history of seizures.

States that there is interpersonal variability in the activity of CYP2D6 (i.e. poor metabolisers).

States that nortriptyline metabolism may be reduced when taking concomitant CYP2D6 inhibitors/substrates.

Sertraline and nortriptyline are mild/weak inhibitors of CYP2D6.Nortriptyline is a major substrate of CYP2D6. Therefore, it is possible that sertraline increases nortriptyline levels.

2.5 Drug interaction information – New Zealand Formulary (NZF)

The drug interaction search tool on the NZF's website provides the following information/advice to healthcare professionals about the concomitant use of sertraline and nortriptyline (11).

Medicines		Explanation	Action	Severity	Evidence
sertraline (systemic) and **nortriptyline** (systemic)		Nortriptyline plasma concentrations can be increased by sertraline. Serotonin syndrome has, rarely, been seen in patients given SSRIs with tricyclics. Nortriptyline (mainly in overdose) has been associated with QT prolongation but an effect is not established. As some other SSRIs are associated with QT-interval prolongation, sertraline is often predicted to have a similar effect, however there is no evidence. Concurrent use might increase the risk.	**Monitor:** Monitor concurrent use for tricyclic toxicity (dry mouth, sedation, confusion). It has been suggested the tricyclic dose should be lowered, and low initial SSRI doses should be used. Be aware of the risks of the serotonin syndrome. Increasing age, female sex, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose to QT prolongation: in their presence consider ECG monitoring.	Severe	Case

Comment: Increased nortriptyline plasma concentrations, serotonin syndrome and QT prolongation described.

The nortriptyline data sheet states that tricyclic antidepressants, including nortriptyline, particularly when given in high doses, have been reported to produce QTc prolongation and arrhythmias.

The sertraline data sheet states that cases of QTc prolongation and TdP have been reported during the post marketing use of sertraline. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Solai et al, Effect of Sertraline on Plasma Nortriptyline Levels in Depressed Elderly (1997)

3.1.1.1 Methods

Using two computerised databases, the authors identified all patients aged 60 years and over who were concurrently prescribed nortriptyline and sertraline by their attending psychiatrist between January 1992 and December 1996 on an inpatient unit at Western Psychiatric and Clinic and at the outpatient multidisciplinary geriatric clinic (Benedum Geriatric Centre) of the University of Pittsburgh Medical Centre.

The authors focussed their analysis on 14 patients (nine inpatients and 5 outpatients) who met the following conditions:

- Sertraline was added to nortriptyline
- Plasma nortriptyline levels had been obtained before and after this addition
- The plasma levels were drawn after a minimum of five days during which all medications (including nortriptyline and sertraline) were held constant.

In all patients, nortriptyline dosages were kept constant after the addition of sertraline.

Sertraline was started at a dose of 25mg or 50mg, given as a single dose in the morning or at bedtime, and initially titrated to 50mg/day in 13 patients and 100mg/day in one patient.

In seven patients, sertraline was subsequently increased from 50mg/day to 100mg/day (N=5) or 150mg/day (N=2).

In inpatients (N=9), plasma samples were obtained in the morning (~12 hours after the evening nortriptyline dose). In outpatients (N=5), plasma samples were obtained in the early afternoon (~18 hours after the evening nortriptyline dose).

In five patients several nortriptyline levels were available after addition of sertraline. In these patients, the nortriptyline level obtained after the longest concomitant treatment with nortriptyline and sertraline was used for the analysis.

Endpoints

- The authors determined the percentage change in nortriptyline levels in the 14 patients relative to baseline before addition of sertraline. They assessed whether the change was statistically significant.

- To test whether the change in plasma nortriptyline was more pronounced in the more extensive CYP2D6 metabolizers, the authors assessed the association between percentage change in plasma nortriptyline level and the initial quotient of plasma nortriptyline level to daily nortriptyline dose (L/D).

  L/D corresponds to the inverse clearance of nortriptyline and therefore reflects the subjects CYP2D6 metaboliser status (lower L/D = more extensive CYP2D6 metaboliser).

- Finally, to test whether a higher dose of sertraline would produce a greater change in plasma nortriptyline level, the authors compared in the seven patients who had further titration of sertraline the percentage change in nortriptyline induced by 50mg/day versus 100 or 150mg/day of sertraline.

3.1.1.2 Results

The mean age of the 14 patients was 72 years. These patients were taking a mean nortriptyline dose of 66mg/day, and were taking a mean of 2.6 prescription medicines. Before the addition of sertraline, they had a mean plasma nortriptyline to dose quotient (L/D) of 1.7.

Individual patient demographics are presented in Table 1 below.

Table 1. Demographic and Clinical Characteristics of Individual Patients

Patient	Age (y)	Sex	Race	Nortriptyline Dose (mg/d)	Duration (d)	Plasma Nortriptyline Level Before Sertraline (ng/mL)	Sertraline Dose (mg/d)	Plasma Nortriptyline Level After Addition of Sertraline (ng/mL)
1	83	F	White	30	30	102	50	142
2	86	M	White	25	12	73	50	66
3	77	M	White	50	6	112	50	102
4	82	F	White	60	10	118	100	109
5	64	F	White	50	30	96	50	74
6	60	F	White	75	9	144	50	106
7	70	M	White	75	24	122	50	121
8	78	F	White	75	5	107	50	138
9	78	M	White	75	5	100	50	78
10	81	M	White	75	7	97	50	120
11	70	F	White	60	10	67	50	101
12	68	F	White	75	13	76	50	79
13	62	M	White	100	21	88	50	121
14	63	F	Black	100	63	59	50	128

Figure 1 below presents plasma nortriptyline levels before and after addition of sertraline. The diagonal line shown represents no change in plasma nortriptyline levels. Patients above the line experienced an increased in plasma nortriptyline levels after addition of sertraline and vice versa. All patients in this figure received 50mg/day of sertraline except for one (100mg/day).

Figure 2 below presents the percentage change in plasma nortriptyline levels and appears to be ordered by L/D value.

Figure 1. Plasma Nortriptyline Levels (ng/mL) Before and After Addition of Sertraline*†

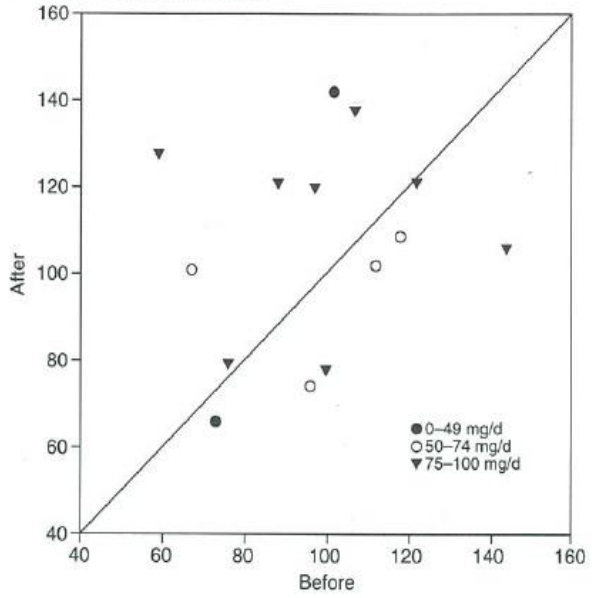
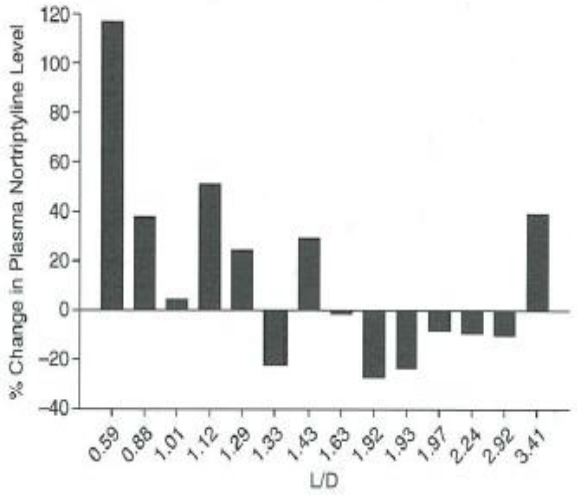


Figure 2. Percentage Change in Plasma Nortriptyline Levels After Addition of Sertraline*



The change in nortriptyline level after addition of sertraline was not statistically significant (median 2%; range -26% to 117%; p=0.3), but there was a trend for this change to be inversely correlated with the initial nortriptyline level to dose quotient (L/D) (Spearman r=-0.49; p=0.07).

In seven patients, plasma nortriptyline level was also obtained before and after sertraline was increased from 50mg/day to 100mg (N=5) or 150mg/day (N=2). While taking 50mg/day sertraline these seven patients had experienced a median increase in plasma nortriptyline level over baseline of 29% (range: -23% to 117%; p= 0.22). With 100 or 150mg/day sertraline, they experienced a median increase over baseline of 40% (range -12% to 239%; p=0.08). The median increases in plasma nortriptyline associated with the lower and higher doses of sertraline were not statistically different (29% vs 40%; p=0.22).

3.1.1.3 Discussion

In 14 elderly patients, typically in their 70s, the authors found that the addition of 50mg/day of sertraline to nortriptyline only had a minimal overall effect on nortriptyline metabolism. It resulted in a median increase in plasma nortriptyline level of only 2%. The authors state that this lack of group effect should be interpreted cautiously given that 2 (14%) of these 14 patients experienced an increase in their plasma nortriptyline levels of 51% and 117% and that these changes would be considered clinically significant.

Of note, there was a trend suggesting that a higher degree of inhibition was observed in more extensive CYP2D6 metabolisers.

Furthermore, escalation in the dose of sertraline from 50mg/day to 100 or 150mg/day in a subgroup of 7 patients was associated with a greater increase in plasma nortriptyline level. This apparent dose dependent difference in metabolic interaction failed to reach statistical significance. A power analysis revealed that an effect of similar magnitude would have been statistically significant if the number of patients had been 10 or higher.

[redacted]

3.2 Company reports

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

CARM case 125559 is the first and only report of a suspected drug-drug interaction (DDI) between nortriptyline and sertraline in New Zealand. [redacted]

Regarding pharmacokinetics, literature suggests that sertraline and nortriptyline have weak inhibitory effects on the metabolic enzyme CYP2D6, which appears to have a role in the metabolism of both medicines. It is also mentioned that there is interpersonal variability in the inherent activity of CYP2D6 (e.g. poor metabolisers) that can affect tricyclic antidepressant metabolism.

Regarding pharmacodynamics, there is information that states that nortriptyline may have some inhibitory effect on serotonin reuptake, although not to the extent/potency in which it inhibits noradrenaline reuptake.

This is in contrast to tertiary amine TCA's (e.g. amitriptyline, clomipramine, imipramine and doxepin) which are described as being more potent serotonin reuptake inhibitors than for noradrenaline.

The advice sought from the Committee is whether the presented evidence is sufficient to warrant inclusion of information regarding a drug-drug interaction in both the sertraline and nortriptyline data sheets.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the presented evidence is sufficient to warrant updates to the sertraline and nortriptyline data sheets. If so how should they be updated?
- Whether there is need for further communication of this issue outside of MARC's Remarks in *Prescriber Update*.

6 ANNEXES

Annex 1: CARM case report 125559

Annex 2: Pfizer company report

Annex 3: Teva Company report

Annex 4: Vigibase reports

7 REFERENCES

1. Buckley NA, Dawson AH, Isbister GK. 2014. Serotonin syndrome. *BMJ* 348: g1626
2. Boyer EW, Shannon M. 2005. The serotonin syndrome. *N Engl J Med* 352: 1112-20
3. Mylan New Zealand Ltd. 2018. *Norpress film coated tablets (10mg & 25mg) New Zealand Data Sheet* April 2018. URL: www.medsafe.govt.nz/profs/Datasheet/n/Norpresstab.pdf (accessed 13 May 2019).
4. Teva Pharma (New Zealand) Limited. 2018. *Arrow-Sertraline film coated tablets (50mg & 100mg) New Zealand Data Sheet* November 2018. URL: https://medsafe.govt.nz/profs/Datasheet/a/arrowsertralinetab.pdf (accessed 13 May 2019).
5. MacQueen G, Born L, Steiner M. 2001. The selective serotonin reuptake inhibitor sertraline: its profile and use in psychiatric disorders. *CNS Drug Rev* 7: 1-24
6. Solai LK, Mulsant BH, Pollock BG, Sweet RA, Rosen J, Yu K, Reynolds CF, 3rd. 1997. Effect of sertraline on plasma nortriptyline levels in depressed elderly. *J Clin Psychiatry* 58: 440-3
7. Lexicomp. 2019. Sertraline: Drug Information. In *UpToDate* URL: www.uptodate.com/contents/sertraline-drug-information (accessed 13 May 2019).
8. Hirsch M, Birnbaum, R.J. 2018. Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects. In *UpToDate* 6 November 2018. URL: www.uptodate.com/contents/tricyclic-and-tetracyclic-drugs-pharmacology-administration-and-side-effects (accessed 13 May 2019).
9. Gillman PK. 2007. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 151: 737-48
10. Lexicomp. 2019. Nortriptyline: Drug information. In *UpToDate*. URL: www.uptodate.com/contents/nortriptyline-drug-information (accessed 13 May 2019).
11. New Zealand Formulary. 2019. New Zealand Formulary. 2019. *New Zealand Formulary v83: Interaction Search* 1 May 2019. URL: https://nzf.org.nz/ (accessed 13 May 2019).