

HPFT GUIDELINE FOR PRESCRIBING TRICYCLIC ANTIDEPRESSANTS (TCA'S)

KEY REMINDERS

- 1. The greatest risk in overdose is with tricyclic antidepressants (TCAs') except for lofepramine.**

When choosing an antidepressant take into account toxicity in overdose for people at significant risk of suicide.

- 2. Prescribing of dosulepin is banned in HPFT.**

Do not switch to, or start dosulepin. Dosulepin and doxepin have the greatest toxicity based on overdose deaths both relative to prescriptions and relative to non-fatal self-poisonings.

- 3. Tricyclic antidepressants are associated with a discontinuation syndrome and should be withdrawn gradually when clinically appropriate.**

People who start on low-dose TCAs and have a clear clinical response can be maintained on that dose with careful monitoring.

- 4. ECG monitoring is required when prescribing TCA's**

ECG monitoring is recommended for people prescribed higher doses of a TCA e.g. doses above 150mg of amitriptyline (in adults <65 years) and doses of 100mg upwards when given in association with other drugs that prolong QT interval, especially with therapeutic doses of antipsychotic medication and methadone.

When the dose is stabilised a minimum of an annual ECG is recommended in the absence of cardiovascular disease. More frequent monitoring may be required if clinically appropriate, when the dose is increased or additional QT prolonging drugs are added to the regimen.

BACKGROUND

The 'National Confidential Inquiry into Suicide and Homicide by People with Mental Illness', examines the circumstances in which people with mental illness commit suicide or homicide, identifies annual trends and uses these to make recommendations to the health service. From the 2012 inquiry, utilisation of a toolkit was offered to mental health services where recommendations could be formulated into quality and safety statements regarding clinical, organisational and training aspects of care. It was highlighted that mental health providers should ensure there is a standard procedure or protocol which takes into account the toxicity of TCAs in overdose when prescribing these drugs.

Self-poisoning is a common method of suicide and often involves ingestion of antidepressants. Information on the relative toxicity of antidepressants is therefore extremely important.

An observational study¹ of prescriptions (UK), poisoning deaths involving single antidepressants receiving coroners' verdicts of suicide or undetermined intent (England and Wales) and non-fatal

self-poisoning episodes presenting to six general hospitals (in Oxford, Manchester and Derby) between 2000 and 2006 was used to assess the relative toxicity of specific tricyclic antidepressants (TCAs), a serotonin and noradrenaline reuptake inhibitor (SNRI), a noradrenergic and specific serotonergic antidepressant (NaSSA), and selective serotonin reuptake inhibitors (SSRIs).

Calculation of fatal toxicity index based on ratio of rates of deaths to prescriptions, and case fatality based on ratio of rates of deaths to non-fatal self-poisonings. Fatal toxicity and case fatality indices provided very similar results (rho for relative ranking of indices 0.99). Case fatality rate ratios showed greater toxicity for TCAs (13.8, 95% CI 13.0-14.7) than the SNRI venlafaxine (2.5, 95% CI 2.0-3.1) and the NaSSA mirtazapine (1.9, 95% CI 1.1-2.9), both of which had greater toxicity than the SSRIs (0.5, 95% CI 0.4-0.7). Within the TCAs, compared with amitriptyline both dosulepin (relative toxicity index 2.7) and doxepin (2.6) were more toxic. Within the SSRIs, citalopram had a higher case fatality than the other SSRIs (1.1, 95% CI 0.8-1.4 v. 0.3, 95% CI 0.2-0.4). (See table in appendix 1).

Of the TCAs, dosulepin and doxepin have the greatest toxicity based on overdose deaths both relative to prescriptions and relative to non-fatal self-poisonings. Venlafaxine appears to be far less toxic than the TCAs but more toxic than the SSRIs and slightly more toxic than mirtazapine. Of the five SSRIs that were examined, citalopram appears to be more toxic than the other four. When prescribing antidepressants the clinician should take account of the risk that may be associated with an overdose, especially in someone judged to be at risk of self-poisoning, as well as relative efficacy, acceptability and possible interactions with other medication and alcohol, and concurrent physical morbidity.

The conclusion was that there are wide differences in toxicity not only between classes of antidepressants, but also within classes. The findings are relevant to prescribing decisions, especially in individuals at risk, and to regulatory policy. A major strength of the study is that two approaches were applied in assessing relative toxicity, the findings of which are remarkably similar. The data on non-fatal self-poisoning have come from three well-established monitoring systems and by using 7 years of data the study has considerable statistical power.

PRESCRIBING

- Prescribers when selecting a suitable antidepressant for an individual service user should carry out a risk assessment and select an appropriate antidepressant with the least risk for that individual considering existing medical conditions, risk of suicide and other drugs prescribed. If a tricyclic antidepressant is chosen then the rationale for choice should be documented in the electronic patient record taking into account the specific cautions, contraindications and monitoring requirements for tricyclic antidepressants (TCAs) (See SPCs for individual drugs including maximum doses on www.medicines.org.uk)
- Consider the potential for interactions if switching to another antidepressant and the nature and duration of the transition. Information on this can be obtained from the SPC of a drug, reference textbooks such as The Maudsley Guidelines, from Medicines Information Departments in hospital pharmacy departments or the Medicines Management Team. The Medicines Management Team contact details are on the TrustSpace web page <http://trustspace/InformationCentre/MedicinesManagement>.
- Other considerations if prescribing a tricyclic antidepressant when deemed to be appropriate for an individual patient
 - Start at low dose and increase slowly. People who start on low-dose TCAs and who have a clear clinical response can be maintained on that dose with careful monitoring.
 - Avoid in severe liver disease
 - Caution in elderly – use lower doses
 - SSRIs generally recommended in cardiac disease.
 - Arrhythmogenic potential of TCAs is dose dependent. ECG monitoring should be considered in those prescribed doses towards the top of licensed dose range and in

those who are prescribed other drugs that increase risk of QT changes (Maudsley Guidelines).

- Drug Interactions (see SPC)
- Swapping and stopping recommendations
- Perform an ECG (NICE) before prescribing TCAs in depressed people at significant risk of cardiovascular disease.
- Lofepramine is NICE's TCA of choice and may have slightly less ADRs than others, blocking the cardiotoxic effects of the main metabolite, desipramine. (Psychotropic Drug Directory, Bazire, 2012)
- Consider the potential for postural hypotension and arrhythmias with TCAs.
- Do not prescribe dosulepin because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.
- Do not prescribe large quantities of TCAs at a time. Consider limited supply, e.g. weekly, with regular follow up and monitoring until risk is no longer present or is significantly reduced.
- TCAs in secondary care mental health services should be started under the supervision of a consultant psychiatrist.
- **NB:** After a TCA overdose, be aware that acute medical wards may want to transfer service users back to HPFT's care sooner than is considered safe. Consider TCAs different pharmacology in overdose i.e. absorption is delayed due to anticholinergic effect; enterohepatic recirculation and a shift to zero-order kinetics due to hepatic enzyme saturation ($t_{1/2}$ may be doubled). Resist early re-transfer and discuss with Medical Registrar.
- Inform service user and carer about common side-effects and time to effect.

CLINICAL MANAGEMENT PLAN

- Care Co-ordinators should be familiar with the risks involved when TCAs have been prescribed. They should liaise with the prescriber and report any side effects.
- There is a small, but identifiable risk, of agitation and increased suicidal thoughts when antidepressants are initiated and the service user and carer should be warned of this and the situation monitored.
- Restlessness, agitation and akathisia are all side effects of treatment and have been linked to suicidal acts. They should not be confused with clinical ineffectiveness and the decision to increase the dose as a result: time to substantial remission may take four weeks in clinical trials.
- If TCAs are prescribed, their use should be documented as a treatment in the service user's care plan.

Appendix 1

Fatal Toxicity: rate ratios and relative toxicity indices for individual antidepressants based on rates of death (suicide and undetermined intent) in England and Wales, and prescription rates in UK

Reference Table 2: Hawton et al, Br J Psychiatry. 2010 May; 196(5): 354–358.

	Both genders		Males		Females	
	Rate ratio (95% CI)	Relative Toxicity Index	Rate ratio (95% CI)	Relative Toxicity Index	Rate ratio (95% CI)	Relative Toxicity Index
Tricyclic antidepressants (TCAs)						
Amitriptyline	11.4 (10.3-12.6)	1.0	20.3 (17.7-23.2)	1.0	7.5 (6.5-8.7)	1.0
Clomipramine	14.1 (10.00- 19.3)	1.2	15.9 (8.4-27.1)	0.8	13.3 (8.8-19.5)	1.8
Dosulepin	36.3 (33.4-39.3)	3.2	70.5 (62.9-78.8)	3.5	23.3 (20.6-26.2)	3.1
Doxepin	28.1 (17.6-42.6)	2.5	60.1 (32.0- 102.7)	3.0	15.9 (7.3-20.1)	2.1
Imipramine	12.4 (8.1-18.4)	1.1	17.0 (8.5-30.4)	0.8	10.2 (5.6-17.2)	1.4
Nortriptyline	9.9 (3.2-23.2)	0.9	-	-	13.3 (4.3-31.0)	1.8
Trimipramine	15.0 (8.0-25.6)	1.3	35.1 (15.2-69.2)	1.7	7.8 (2.5-18.1)	1.0
All seven TCAs	18.8 (17.7-20.0)	1.7	33.7 (31.0-36.5)	1.7	12.6 (11.6-13.8)	1.7
SNRI: venlafaxine	5.3 (4.2-6.6)	0.46	8.7 (6.4-11.6)	0.43	3.5 (2.5-4.9)	0.47
NaSSA: Mirtazapine	3.6 (2.1-5.7)	0.32	4.1 (1.808.1)	0.2	3.3 (1.6-6.0)	0.44
SSRIs						
Citalopram	1.7 (1.3-2.3)	0.15	3.3 (2.2-4.7)	0.16	1.0 (0.6-1.6)	0.14
Fluoxetine	0.5 (0.3-0.9)	0.05	0.6 (0.2-1.3)	0.03	0.5 (0.3-1.0)	0.07
Fluvoxamine	-	-	-	-	-	-
Paroxetine	0.5 (0.2-0.9)	0.04	1.1 (0.4-2.2)	0.05	0.2 (0.05-0.6)	0.03
Sertraline	0.7 (0.3-1.3)	0.06	1.1 (0.3-2.7)	0.05	0.5 (0.1-1.2)	0.06
All five SSRIs	0.9 (0.7-1.1)	0.08	1.6 (1.2-2.1)	0.08	0.6 (0.4-0.8)	0.08

TCAs= tricyclic antidepressants, **SNRI**=serotonin and noradrenaline reuptake inhibitor, **NaSSA**=noradrenergic and specific serotonergic antidepressant, **SSRIs**=selective serotonin reuptake inhibitors

References

Hawton et al. Br J Psychiatry. 2010 May; 196(5): 354–358

Safety First: Five Year Report of the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness (2001).

The National Suicide Prevention Strategy for England (2002)

Preventing Suicide: A Toolkit for Mental Health Services (2003 – updated 2009)

NICE: Depression in Adults: CG90 (2009)

NICE: Depression with a Chronic Physical Health Problem CG91 (2009)

Self Harm, Suicide and Risk Helping People who self harm - Royal College of Psychiatrists (2010)

National confidential Inquiry into Suicide and Homicide by People with Mental illness Annual Report: England and Wales July 2012 – The University of Manchester.