Clomipramine: Potent SNRI Anti-Depressant

by Dr Ken Gillman | Last updated Mar 23, 2019 | Published on Oct 11, 2015 | Anti-Depressants, SNRIs, TCAs

Introduction: 50th Birthday Tribute

Clomipramine is usually thought of by doctors as a treatment for obsessive-compulsive disorder (OCD). But it is a potent antidepressant with dual SNRI action (see tables of comparative receptor affinity data below). There is better evidence for clomipramine's superior effectiveness for refractory depression than for any other drug. The frequency with which it is ceased because of side effects is no greater than SSRIs, and probably less that venlafaxine (see below). It is less toxic in overdose than venlafaxine (see my TCA review for further details (1)).

So with all those positive attributes, why do so few doctors use clomipramine in depression? First, ignorance about it; second, an accident of history*; third, profits and advertising (see separate commentary on the rising cost of generic drugs**).

* It came in around 1966 (2-5), after imipramine and amitriptyline were established and it was the first drug effective in OCD which became its niche, consequently most doctors did not think of it as an antidepressant.

** For a long time generic clomipramine (it came out of patent many years ago) cost 22 cents per tablet, just recently it has soared to $8. That is capitalism for you. Gillman's Aphorisms, No. 13. Capitalism is bad for your health, bad for science and bad for rational discourse.

The endlessly repeated generalisation that TCAs have more side effects and are more toxic than SSRIs, or other newer drugs, is simply wrong. That generalisation is founded on a basic error of logic. 'TCAs', in so far as they can be usefully lumped together meaningfully as class are defined by their physical structure (tricyclic- three rings) not by their pharmacological properties, which are quite varied. Therefore to compare 'TCAs' with other similarly misconceived classes like SSRIs is akin to trying to compare a basket of mixed vegetables with a basket of mixed fruits.

By 1980 there were various specialists in refractory depression in the UK who regarded it, along with tranylcypromine, as more potent than other drugs (6-9). In his book 'The Antidepressant Era' Professor David Healy makes the same observation. I have had extensive experience using it where other antidepressants have failed and definitely concur with the view that it has superior efficacy.

A short aside is relevant. When venlafaxine was introduced in the late 1990s I still had many patients on clomipramine, which was in those days the only SNRI (Although I was using the SNRI combination of sertraline + nortriptyline increasingly frequentl). Patients in private practice often want the latest drug because they have been told how good it is, so I had a number of patients who wished to swap to venlafaxine. I took careful note of their progress and it was quite striking that out of the first 20 or so almost all of them came back within a month or two wanting to go back on clomipramine because they found venlafaxine

substantially less effective (and, then, a fraction of the cost). Without going into the intricacies of scientific methodology it is easy to appreciate that dealing with a more pure sample of drug-responsive patients (i.e. people have already responded to clomipramine) produces a clearer picture of the relative potency of the two drugs, especially when the same patients regain their previous improvement on going back on clomipramine. That initial experience, combined with subsequent experience, persuaded me that venlafaxine was less effective by a considerable margin.

The top four websites returned by my recent Google search about clomipramine (see 'link sites' below) are generally incomplete and misleading. Wikipedia is often a satisfactory place to start, but even the Wikipedia entry for this drug leaves something to be desired. Wikipedia does quote my review of the TCAs (1), but it then goes on to contradict some of the information with references that are inappropriate or out of date. Ah well! One can only try.

So, will readers please set about correcting that by promulgating this commentary to make it rank higher than these other less satisfactory sources! By doing that you will help others to find better information more quickly, indeed you might even save a life.

History

It seems ironic that despite all the new drugs that have arrived in the last four decades the best evidence for superior efficacy and/or a unique profile of action is for the oldest ones (e.g. clomipramine, clozapine and lithium).

Clomipramine was the first, and for some while the only drug (till fluoxetine ~1986), that was effective for obsessive compulsive disorder.

The fact that it is effective for OCD, where the previously available TCAs like amitriptyline and imipramine were not, is one important piece of evidence indicating clomipramine alone is a clinically effective SRI. One still frequently reads the opinion that TCAs generally are dual action SNRIs. There are many good reasons to confidently reject that proposition, these are discussed in detail in various of my published papers, especially (1, 10).

I list here, for interests sake, the various early references I have found concerning clomipramine: (3, 5, 11-22).

Clomipramine has now, as of 2015, been in use for 50 years; for all that time it has possessed the three properties that are promoted to increase the sales of newer, and expensive, drugs: viz. it is a serotonin reuptake inhibitor and a noradrenalin reuptake inhibitor and a 5-HT2A blocker, and has a modest but useful sedative effect via H1 antagonism (23).

Phamacokinetics and 'Therapeutic' Plasma Levels

All TCAs are highly lipid soluble and are rapidly absorbed (peak levels are usually reached within 2 hours) with extensive tissue distribution (volumes of distribution from 5-20 L/kg. (24, 25). Plasma concentrations for therapeutic effect are stated

by various sources to be around 50 – 300 ng/ml (molecular weights range from 263 to 314). As a guide a 75 mg daily dose may be expected to produced steady state concentrations of clomipramine between 30 and 200 ng/mL. Older studies suggested an optimal therapeutic effect was with the sum of clomipramine and demethylclomipramine between 200-400 ng/ml (26). The elimination half-life estimates exhibit wide variation e.g. 19-37 hours (Drugbank), CYP2C19 and 2D6 gene variations play a big part in that (see below).
However, it is important to appreciate that these therapeutic ranges are based on rather poor evidence and more recent data on TCAs suggest at least some of them may be incorrect by at least one order of magnitude, e,g. standard doses for desipramine were almost certainly much too high which is part of the reason it has been removed from the market in many jurisdictions: the DDD (defined daily dose- which governs how much is in one packet) was high, so when people took a whole packet of it as an OD, they were effectively taking a much larger OD compared to other drugs. Hence it appeared very toxic. Had it been marketed as much smaller 5 – 10 mg size tablets, more like reboxetine (which has about the same affinity for the NAT), it would likely have worked just as well but appeared much less toxic!
For clomipramine the serotonin transporter (SERT) occupancy, using Positron Emission Tomography (PET) in humans, with a plasma concentration of only 1.42 ng/mL produces about 80% occupancy of SERT (27), see 'PET' studies below. Note the usually stated therapeutic range of plasma levels is in the range of 50 – 400 ng/ml. Again, like desipramine, one to two orders of magnitude different!
Szegedi et al. used fluvoxamine (as did I occasionally) in combination treatment with clomipramine to 'level the field' re P450 variation and thus keep the ratio of CMI/D-CMI closer to unity (28). It works, but it troublesome and not without risk. I found it preferable to just use my good old sertraline + nortripyline combination.

Receptor Profile and Efficacy

The newer so-called SNRI compounds, venlafaxine (and its 'badge engineered' derivative metabolite desvenlafaxine) and duloxetine may not be as effective at simultaneously blocking SERT and NAT. That is because their ratio of potency at those two sites is very different (see table), which suggests that at any one dose their effect at one site will probably be too great, and at the other too little. There is still doubt about how venlafaxine works and how well it works; it is a relatively weak noradrenalin reuptake inhibitor (see my TCA review) that has only a weak effect on the tyramine pressor response (29) (75 mg does not alter the tyramine pressor response at all, and higher doses only a little).
Clomipramine is metabolised (mostly via 2C19) into desmethyl-clomipramine which, like desipramine (which is desmethyl-imipramine), is a potent noradrenalin reuptake inhibitor. NB Clomipramine is the chlorinated analogue of imipramine (early publications referred to it as 'mono-chlor-imipramine).

Since both clomipramine and desmethyl-clomipramine are present in tissues in pharmacologically active concentrations the net effect of clomipramine is that of an SNRI.
It is useful at this point to enumerate why clomipramine may be more potent than the newer SNRI drugs. Quite apart from the fact that the ratio of the two re-uptake effects (SERT and NAT) is closer to 1 to 1 than the other drugs (see table), which is probably a good thing, it also has other effects which may be relevant. These are the sedative effects via H1 blockade, anti-muscarinic effects, and 5-HT2A antagonistic effects.
It is worth observing also that the SNRI combination of sertraline with nortriptyline is in my view superior to sertraline with reboxetine (a 'pure' NRI drug). That suggests the extra properties enumerated above (and which are possessed to a similar degree by most TCAs, including nortriptyline) do indeed make a difference and that in turn suggests why clomipramine would be superior to venlafaxine.
These tables below are taken from my TCA review paper (1).
NB If comparing these figures with other data consider only human cloned receptor data (HCR) data, much of the older data are not HCR and are not comparable. Further discussion about this may be found in the commentary 'Understanding Receptor Affinity Data' link
https://www.psychotropical.com/understanding-receptor-affinity-data/

Receptor profile, Ki in nmol/L, of TCAs and comparator drugs: uptake inhibition and receptor antagonism (human cloned receptor data)

Drug	Reuptake inhibition		Post-synaptic receptor antagonism			
	5-HT	NA	H1	A1	Musc	5-HT2A
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	3.2	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

Table legend
All data has been extracted from PDSP K_i data base, (except * Richelson (30)). 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, approximate mid-range values are given (Table 2 gives ranges). Receptors: H1 Histamine type 1, Musc acetylcholine muscarinic, A1 alpha1 adrenergic.

Human cloned receptor data, K_i in nmol/L, and TYR30, relating to dual action

Drug	TYR30	NA	5-HT	NA/5-HT
SSRIs (for comparison)		>1000	0.1-20	> 1:1000
Amitriptyline	N/A	19 – 102	2.8 – 36	~1:1.5
Nortriptyline	+++	1.8-21	15-280	

Clomipramine	N/A	54	0.14-0.3	~2:1
Desmethylclomipramine*	+++	<1*	–	
Imipramine	N/A	20 – 142	1.3 – 20	~1:2
Desipramine	+++	0.63 – 8.6	22 -180	
Duloxetine**	0	7.5-20	0.8-3.7	10:1
Venlafaxine**	0/+	1,420–6,300	7.5-145	200:1
Desvenlafaxine***	–	3,500	40	100:1
Sibutramine	–	No HCR data	No HCR data	
Milnacipran**	–	151-200	68-123	1.7:1

Table legend
TYR30: tyramine pressor response *at recommended therapeutic dose*, degree of reduction placebo/NRI: +++ = nearly complete inhibition i.e. potent NRI effect. K_i data has been extracted from PDSP K_i data base (accessed June 2006) http://pdsp.cwru.edu/pdsp.asp , except: *approximation from Human cortex data, no HCR data available. **additional HCR values from (31). For human in vivo considerations the TCAs are grouped as pairs (i.e. amitriptyline is metabolised into nortriptyline, and clomipramine to desmethylclomipramine and imipramine to desipramine: for TYR30 N/A indicates that in vivo, parent drug cannot be present without greater effect from more potent NRI metabolite). The NA/5-HT ratio is approximated because varying in vivo levels of metabolites occur. Clomipramine is the most potent, and the only available drug with combined affinities for both systems of less than one. It is unlikely that varying drug levels in different tissues would compensate for the extreme weakness of venlafaxine (and desvenlafaxine) as an NRIs.
***Only 1 set of values, from Deecher et al. (32).

Efficacy

There is evidence from the 'DUAG' studies (33-36)) that clomipramine is an antidepressant of superior efficacy. It is also effective for obsessive compulsive disorder (possibly more so than SSRIs (37)), generalised anxiety disorder, phobias and panic attacks, narcolepsy/cataplexy (38-40), not to mention migraine.
The value of experts and experience is always to be regarded with caution (see commentary Freud, Fraud and the Delusion of Experience), but with that caveat in mind one may still note that a number of psycho-pharmacologist that I have known over the years agree that clomipramine is an antidepressant of superior efficacy. In his book 'The Antidepressant Era' Professor David Healy makes the same observation.
There is one further observation concerning the superior efficacy of clomipramine that I made many years ago, and for which I have never seen a satisfactory alternative explanation that would contradict my view. It is apparent that of all the patients treated with antidepressants the chance of somebody taking an overdose varies by at least ten-fold between different drugs (these are suicide attempts, not deaths, so this has nothing to do with a drug's toxicity).
If the number of people who take an overdose (not the number of deaths from OD), for every hundred thousand scripts issued, is very substantially less for one particular drug then one obvious explanation is that the drug is a more effective antidepressant and greatly reduces suicidal urges: an excellent property for an anti-depressant!. That applies to clomipramine which appears with about 1/10 the frequency expected, compared to other TCAs, and other antidepressants.
One different explanation of this that I recall being proffered in the past was that it was because clomipramine was used for obsessive-compulsive disorder, and such patients attempted suicide much less frequently than those with depression. That is probably true, but OCD is such a rare disease (as a primary disorder in the absence of depression) that the number of such patients represented in the clomipramine sample would be very small indeed compared to the total number of patients to whom scripts had been issued. It is obvious that could not possibly account for a difference in the attempted suicide rate that is around ten-fold.
The most parsimonious explanation is that if you take clomipramine you are far less likely to feel suicidal and act on that feeling: that would appear to indicate strongly that clomipramine is a better antidepressant.

Positron Emission Tomography (PET) PET Studies

Positron Emission Tomography (PET) studies of binding to transporters (e.g. SERT & NAT) and receptors in humans(27, 41) confirm what the receptor potencies below would suggest, that small doses of as little as 10 mg clomipramine are effective at substantially inhibiting the serotonin transporter: however some of these results are inconsistent (42-45) and it is premature to draw firm conclusions.
Suhara et al. "Occupancy of 5-HTT increased in a curvilinear manner. Even 10 mg of clomipramine hydrochloride showed approximately 80% occupancy, which was

comparable with that of 50 mg of fluvoxamine maleate. Estimated median effective dose (ED50) of clomipramine hydrochloride was 2.67 mg for oral dose and 1.42 ng/mL for plasma concentration; those of fluvoxamine maleate were 18.6 mg and 4.19 ng/mL, respectively".

NAT occupancy, for Clomipramine (in non-human primates) 50% of NAT was occupied, at a dose of 0.44 mg/kg producing a plasma level 25 ng/ml, and for desmethyl-clomipramine 0.11 mg/kg and 4.4 ng/ml (41). i.e. Clomipramine itself appears, *in vivo*, to be a significant NRI.

SERT occupancy in humans: clomipramine at a plasma concentration of 1.42 ng/mL produced 80% occupancy of SERT (27).

Side Effects and Toxicity

Although all TCAs can have troublesome side effects, as can all effective drugs, it is pertinent to note that there is, at worst, a 3% difference in side effect discontinuation rates between TCAs and SSRIs (see Anderson (46)). Some studies suggest no difference at all (47). Paradoxically, for older patients any possible differences may be smaller. Most data come from (SSRI) sponsored trials so are likely to be biased in favor of SSRIs- a fact strongly substantiated by the absurdly low estimates of retardation of orgasm in all company sponsored SSRI drug trials. Indeed, since lengthening of the time taken to reach the point of orgasm is a centrally (brain) mediated effect of increasing 5-HT concentrations it is not a 'side effect' at all, but a reliable indicator of the drugs' presumed main therapeutic effect.

A key consideration which can sometimes be lost in this market-orientated side-effects debate is that a drug with less side-effects (or lower toxicity in over-dose) is not an advance if it is less effective. In my view, this sums up the position of many new drugs, including SSRIs, which are less effective for serious depression.

Antidepressants: a Minor Contributor to Suicide Deaths

The key problem in serious depression is that illness severity and duration increase the risk of suicide. The life-time risk of death by suicide is around 10% (48, 49). The problem is not death caused by the toxicity of prescribed anti-depressant drugs when taken as an overdose.

If patients get better from the depression they are less likely to commit suicide. The comparatively much lesser problem of the potential toxicity of drugs in overdose (and claimed differences between various drugs) is appropriately dealt with by good clinical management of any seriously ill patients. Choosing a marginally less toxic-in-overdose drug is not the first-stop option. Good clinical management involves seeing them more frequently and not prescribing potentially fatal quantities of drugs. Incidentally, I am quite sure most doctors, including specialist psychiatrists, would not know what the potentially fatal dose of the particular drug they are handing out actually was*.

*For instance: citalopram has a rather higher FTI than any other SSRIs, yet it has been one of the most frequently prescribed ADs of the last decade, even though there is no evidence it is 'better'.

A major weakness of the argument that promotes preferential prescription of (supposedly) less toxic drugs is that a only a small minority of patients who commit suicide use their prescribed drugs to do so; studies show that less than 10% of deaths from suicide were from the prescribed AD drug (50, 51). All studies show that drugs generally, whether prescribed or not, whether anti-depressants or not, make a minor contribution to the number of deaths from suicide in those suffering serious depression (52-54).

So the notion that doctors should give over-riding consideration to prescribing less toxic drugs* is a poor, even specious, argument based on poor suppositions that are sometimes disingenuously represented**. It is a good scare tactic and sales pitch though – how could I even think that!

* Not only are the reliability of such statistical data poor but the actual differences between most relevant drugs are small (see FTI data below). In other words, the likely degree of error in the data is greater than the differences being pontificated about.

** A very silly paper, co-authored by an underemployed barrister-at-law, argued this point aggressively a while ago (55) and put forward the ridiculous proposition that to prescribe drugs said to be marginally more toxic was medical negligence in law! A novel form of ambulance chasing!

Clomipramine is less toxic in over-dose* than most other TCAs (nortriptyline may be the least toxic TCA) and about the same as venlafaxine (25, 56-58).

* The Fatal toxicity index (FTI) is the number of deaths per million prescriptions issued in a defined population. For clomipramine it is around 12 per million, nortriptyline is around 5 per million, venlafaxine is around 13 per million.

Initial Dose and Rate of Dose Increase

Providing the dose of clomipramine is adjusted carefully it is tolerated well by most patients; blood levels (of all TCAs) are often useful in optimising the dose (59, 60), although it is a little surprising that many psychiatrists never measure them (e.g. see http://www.preskorn.com/columns/9811.html).

The dose should be judged according to the patients' improvement and the degree of side effects experienced, not just the blood levels*, and CYP450 status is only one of various considerations concerning dosage.

Starting doses in the range of 10 to 25 mg daily (for 'little-old-ladies' around 5 mg) are appropriate and should be taken as a single dose at night (because of its longish half-life, and contrary to a number of extant recommendations, it is pointless to take it three times a day).

Experience and evidence suggest it is prudent and worthwhile to give smaller doses, 25 – 75 mg, plenty of time, 6 – 8 weeks, to show their potential benefits before escalating further.

*Note, when blood levels are taken these must be done 12 hours after the dose is taken, i.e. around 9 o'clock in the morning. Steady state may take as long as two weeks after initiation and dose changes.
The old pharmacologists adage of 'start low, go slow' is especially appropriate. Premature and hasty increases of dose are a common cause of therapeutic failure, so persistence and patience are often rewarded. However, vacillation and indecisiveness are equally to be avoided. There is little excuse for the common story I am told of people with partial response who have been kept on a low dose for months on end without a trial of a higher dose. It is surprising how many doctors are illogical, inconsistent, and careless concerning the monitoring, follow-up and adjustment of drug doses. Monitoring of blood pressure to assess the degree of postural hypotension is often helpful in guiding the dosage increases, especially if blood levels are not easily available or affordable.

Influence of CYP450 (P450) Enzyme Status on Plasma Levels and Dose

Amitriptyline, clomipramine, and imipramine are demethylated by CYP2C19 (a sub-type of P450) into active metabolites. These active metabolites, (amitriptyline is converted to nortriptyline, imipramine is converted to desipramine, and clomipramine is converted to desmethyl-clomipramine), are formed by dehydroxylation via CYP2D6 (to less active or inactive metabolites).
Some P450 sub-types ('isoforms'), including both 2D6 & 2C19, are very polymorphic (i.e. they have many mutations, with slightly different structures and levels of activity) which may therefore have different effects on the rate of metabolism and therefore on blood levels.
CYP2D6 therefore has a strong influence on levels of nortriptyline, desipramine, and desmethyl-clomipramine.
The Clinical Pharmacogenetics Implementation Consortium have recently updated guidelines for the dosing of Tricyclic Antidepressants using patients' individual CYP2D6 and CYP2C19 genotypes (60).
However, there is so often a catch, and a little knowledge is a dangerous thing. There are many possible variants (mutations) of these enzymes (see this link). It is only for a few of them, and with particular drugs, that we can usefully predict the effect on blood levels. A mutation that effects the metabolism of metoprolol (a common test drug for assessing 2D6 function) may affect another 2D6 substrate differently; so the predictability for levels of other drugs is uncertain.
Beware of doctors, and companies offering testing services (often expensive), who think they understand more about this than they actually do. Simply measuring your actual plasma (blood) level may well be simpler, cheaper, more accurate, and more informative.
If one was using nortriptyline which is relatively unusual drug, in that it is almost entirely dependent on 2D6 for its metabolism, which produces an inactive metabolite, then knowledge of 2D6 status is of some use.

2D6 poor metabolizers (~10% of patients) are those individuals carrying two loss-of-function alleles, i.e. they have the diplotype *2/*2, or *2/*3, or *3/*3. These mutations (genetic variants) are non-functional and that individual is thus unable to metabolise (break down) nortriptyline (or desmethyl-clompramine). In these instances starting with a dose of 10 – 25 mg would be prudent.
However most drugs, including clomipramine, are not quite so simple. They are often dependent on more than one P450 isoenzyme for their metabolism, and are metabolised into active metabolites (sometimes more than one), in this case desmethyl-clomipramine, so the complex interplay of different factors, in many instances, is unlikely to be easily predictable.
The Clinical Pharmacogenetics Implementation Consortium recommendations in the Hicks paper (61), the content of which I suspect most clinicians are going to have trouble assimilating and utilizing, are complex and would rarely alter clinical practice (as set out herein).
Good clinical practice already dictates 'start low and go slow' and the prominence of side-effects and response to a gradual increase of dose (allowing for the time taken to reach steady state), combined with monitoring the degree of postural hypotension, is what would guide me. That course of action is only rarely going to be altered by the results of genetic testing.
There is one (rather rare) situation where a genetic test result would be useful: if an individual was an ultrarapid metabolizer for 2C19 they would have low levels of clomipramine (which would be rapidly converted to desmethyl-clomipramine); if they were also a 2D6 poor metabolizer that higher level of desmethyl-clomipramine would be metabolized slowly and lead to accumulation of much higher than usual levels. Ultrarapid metabolizers for 2C19 constitute 5–30% of patients and the gain-of-function allele causing this is represented as *17: so if there is one functional allele and one gain-of-function allele i.e. diplotype *1/*17, or two gain-of-function alleles, diplotype *17/*17, then that individual will be an ultrarapid metabolizer of clomipramine.
So, if the testing shows 2C19 diplotype *1/*17/ or *17/*17 and also 2D6 diplotype *2/*2, or *2/*3, or *3/*3 then there is a potential problem and care in dosing would be required.

Resources and Links

www.drugs.com
https://en.wikipedia.org/wiki/Clomipramine
www.nps.org.au
www.medicinenet.com
The Human Cytochrome P450 (CYP) Allele Nomenclature Database-
http://www.cypalleles.ki.se

Prominent websites returned by a Google for a search about clomipramine

www.drugs.com

https://en.wikipedia.org/wiki/Clomipramine
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