Quetiapine: The miracle of Seroquel

by Dr Ken Gillman | Last updated Mar 23, 2019 | Published on Apr 10, 2017 | Anti-Psychotics

Introduction

Doctors have been prescribing this incredible drug more and more as they believe it to be of use in such a wide variety of conditions. It was first approved for schizophrenia (and therefore called an 'anti-psychotic') but then it seemed helpful in cases of depression, of all kinds, so is also regarded by many as a 'mood stabiliser' and anti-depressant and anti-manic agent. More recently still, it has been used in generalised anxiety disorder and sleep disturbance (and who does not suffer from those?), also for disturbed behaviour in old people, especially those in nursing homes: there are so many of them and they can be so 'time-intensive' and they will keep trying to get up out of their chairs (so much better if they just sleep their time away). We must not forget the little ones, what about ADHD, or whatever they have that is making them a pest. Yes, quetiapine may be the answer. And, there is more: it is finding a use in PTSD, anorexia nervosa, OCD, borderline personality disorder: indeed, there is an argument for just putting in the water supply.

The pharmaceutical company continue to be pleased with the sales, which I believe are now getting close to $100 billion; if only that pesky patent law could be altered, surely someone can come up Trump(s) on this one! that would be a Tr(i)ump(h). He might oblige.

I hope and trust no-one has read this far without realising that I am employing humour and sarcasm, because if I did not I would be so enraged about the whole obscene farce surrounding quetiapine that you would have been reading a tirade of abuse against the drug company, my gullible colleagues, and all the people involved in publishing the third-rate so-called 'scientific papers' about this drug. No surprise; I am about to expound on just how bad and how dishonest it all is. Who remembers 'Flanders and Swan'? Even the young ones may have heard the 'Hippopotamus' song 'Mud, mud, glorious mud': in this context, I am reminded more of their witty song about the newly discovered multi-purpose vegetable called the 'Wompom', which provides everything imaginable

'… the flesh in the heart of a wompom has the flavour of porterhouse steak,
and the juice is a liquor that will get you higher quicker,
and you'll still get up next morning when you wake.

Take a break and listen, and if you get angry about the stuff below, listen again, it will bring a smile back.

https://www.youtube.com/watch?v=CsaNgsoQcO4

I choose the words 'incredible' and 'believe' in my first sentence because, as the old saying goes 'If it sounds too good to be true, it is too good to be true'. Science is about **replicatedevidence**, not belief, or impressions created by promotion and

spin doctors. Doctors are especially susceptible to spin precisely because they think it affects others, but not them.

Unbelievable claims: ‘post-truth’ era science

There is neither good evidence that quetiapine has any useful pharmacological effect other than increased appetite, weight gain and sedation, nor that its hundredfold price differential over other available drugs (e.g. promazine or doxepin) is justified. These effects result from its most potent pharmacological property, by far, H1 antagonism. In other words, it is good for hay-fever! (see table).

Quetiapine’s potency is about 100 times greater at H1 vs D2 receptors: if it was marketed on the same basis as the SSRIs it might called a **super-selective histamine blocker** (SSHB)! I have been surprised while doing this update of quetiapine that none of the papers I have reviewed even mention, never mind discuss, its H1 potency: we certainly are living in the ‘post-truth’ era!

Here is the seminal paper linking weight gain and H1 potency from Solomon Snyder’s lab (1), and others (2-4). If you are a psychiatrist, and you do not know who Snyder is then you should be ashamed of yourself https://en.wikipedia.org/wiki/Solomon_H._Snyder

There is no evidence or reason for supposing quetiapine possesses useful or unknown new properties (see ‘fast-off’ below). Indeed, from a pharmacological point of view this drug regresses us to the dawn of psychopharmacology in the 1940s (see table below).

It is the first drug in the modern era to be prescribed widely for sleep, anxiety, depression and schizophrenia: it is either a miracle, or the most stupendous con-job ever perpetrated on patients, and the eternally gullible psychiatric fraternity.

Part of the reason the link between weight gain and psychotropic drugs (many have H1 potency) was slow to be recognised was that very few doctors bothered to weigh people, and if they did they never used properly calibrated accurate scales: I always weighed patients at every visit (on proper accurate scales) and it was obvious with the old TCAs that those with higher H1 potency caused more weight gain, like-wise with the anti-psychotics. I remember writing something about this around twenty years ago — I was astonished to find that most of the papers relied on patient self-reports of weight gain! That gives a vivid insight into how hopelessly unscientific most psychiatrists are — I wanted to shout at them, ‘haven’t you got a f**king set of scales’! One fellow took my breath away when he replied that proper scientific scales were too expensive.

Mutton dressed as lamb

A brief explanation may help. Many papers on the history of psycho-pharmacology relate how the tricyclic nucleus of the aniline dye, methylene blue, led to the discovery — France, the **1940s** — of the first antipsychotic drug, chlorpromazine, and its’ structural analogues, the first tricyclic antidepressant (imipramine), and the first generation of antihistamines, promethazine (good old

‘Phenergan’). All these ‘tricyclic’ drugs are still on the market, including the ‘proto-typical’ promazine.
Promazine was regarded as too weak to be useful, and as is obvious from the names, led to the development of chlor-promazine (Largactil), the first antipsychotic drug. Adding electro-negative elements such as chlorine increases the potency of many tricyclics — hence, add chlorine, and imipramine becomes the much more potent ‘chlor-imipramine’, viz. clomipramine (Anafranil).
The table below gives the **well-replicated** pharmacological data demonstrating clearly that quetiapine is no different to promazine; on the face of it, we have returned to the 1940s.
Some drug, some progress.
Remember Winston? ‘Some chicken, some neck’. Ottawa 1942
https://www.youtube.com/watch?v=y6JxSHmVB5g

Table of Affinities (Ki nM)

	D2	5-HT2A	H1
Promethazine	250	170	1
Promazine	200	15	2
Chlorpromazine	2	5	2
Quetiapine	500	150	7
Doxepin	350	25	0.2

Data from the PDSP database (approximate means from several sources, not all HCR data). https://kidbdev.med.unc.edu/databases/pdsp.php
Most drugs seem to need low single figure affinity potency (i.e. <10 nM) to produce clinical effects. An affinity of 500 nM is regarded as insignificant.
Note: For structure and 3D configuration See http://www.drugbank.ca/

What does it all mean?

What does it all mean? Much could be written about this; however, the rule of parsimony suggests that the simplest explanation is likely to be correct: the simplest explanation is that since there is so little pharmacological difference between promazine and quetiapine the likelihood of there being any substantial

difference in their therapeutic efficacy in schizophrenia, or anything else, is small. I would say close to zero.
The same must be said of quetiapine's supposed benefits for treating, or augmenting, depression. In that context, there is no basis for supposing it to be superior to doxepin, which is a useless anti-depressant, but the most potent anti-allergy drug on the world market — still, after 50 years!
The potencies in the table mean that for quetiapine we would expect no substantial effect in humans, other than H1 antagonism (viz. increased appetite, sedation), unless it is used in doses of around 1,000 mg daily, close to its toxicity threshold (the max recommended doses are between 300 – 800 mg, depending on indication).

A quick lesson from history

Incidentally, I have put doxepin in the table because it is similar and contains historical precedents and lessons. It was of course originally classified as a tricyclic antidepressant, despite its' noradrenaline reuptake inhibitor potency being so weak as to be of no consequence whatsoever. It is one of the most potent antihistamines known, about equipotent to mirtazapine. That property (H1 antagonism) inevitably makes it increase appetite (promoting weight gain) and produce sedation, sleepiness and reduction of anxiety. Hence, over the decades, it has been used as a hypnotic and anxiolytic: indeed, around the time of my TCA review paper, which expounded on the usefulness of doxepin, ((5), see table 5), it was reformulated and marketed as a hypnotic in the USA (Silenor). There are dozens of similar drugs with antihistamine activity that have been used for appetite stimulation and sleep, as well as allergies, over the last 50 years (diphenhydramine, doxylamine, cyproheptadine, trimipramine, hydroxazine, promazine, promethazine, carbinoxamine, dimenhydrinate etc.).
For many years (mis-guided) psychiatrists used doxepin as an antidepressant, and some may still think it works: its most prominent clinical effect was of course sleepiness and weight gain which is inevitable because of its extremely potent H1 antagonism. It was useless as an antidepressant, except that it improved appetite, sleep and anxiety symptoms. That produces substantial improvements in depression the rating scales (see below) used to assess depression and hence allows it to be 'misclassified' as an antidepressant, **even though it does not improve the core symptoms of anergia and anhedonia**. This paragraph could be repeated with quetiapine (or mirtazapine) substituted for doxepin. It took psychiatrists 30 or more years to realise doxepin was useless, I don't suppose they will become enlightened about quetiapine any more quickly, since there is no reason to suppose the present generation are any smarter than the previous one. Indeed, they probably suffer from the disadvantage that they are even more influenced and indoctrinated by drug company 'education' and promotional material than previous generations.

Is there an explanation?

It is certainly possible to produce all sorts of far-fetched pharmacological theories that might account for a possible different in effect of Promazine and Quetiapine, even though current assay techniques indicate they are so similar. However, to be convincing such evidence would have to be reliably replicated by different research groups and a plausible mechanism linking any such effect with well-established clinical differences would need to be demonstrated. As those who have read a few of my commentaries will know, all sorts of theories have been advanced about all sorts of things in psycho-pharmacology over the last 50 years. Few have proved 'true', even when they emanated from independent sources. All the RCTs originate from the pharmaceutical manufacturer and are thus even less likely to be corroborated and substantiated by additional independent research (6-8).

The evidence adduced in relation to the supposed therapeutic effect, never mind superiority of, quetiapine is pathetic; but more of that later.

The key issue is this: is there any sound evidential basis for supposing quetiapine is, despite being so-like promazine pharmacologically, somehow magically different in a way we do not yet understand, that confers advantage? Pigs might fly.

The 'fast-off' idea

The main explanation put forward is the so-called 'fast-off' idea (see also discussion of another unconvincing 'explanation' re 5-HT2A receptors here). This idea suggests that the key difference with atypical antipsychotics is that they dissociate from their binding with the D2 receptor much more quickly, like 100 times more quickly, than the traditional antipsychotics (9, 10). Put simply, the evidence for this is unconvincing and not well replicated and the techniques used to establish this are new, uncertain, and of unproven reliability. The most recent research suggests little or no association between 'fast-off' properties and 'atypical' characteristics, whatever they are conceived to be (11).

It is also notable that most of the publications on this topic seem to come from one author, Seeman: that should always make one sceptical, just like Meltzer and the 5-HT2A story. It is premature to justify, or base, any clinical actions on such a nebulous notion. The notion that the weaker the D2 binding, the better it works, reminds one of homeopathy!

A medline search for 'atypical antipsychotics' and 'fast-off' yields only 6 results since Seeman's 2002 paper: one would think, after 15 years, if there was mileage in this idea, that the drug company would be throwing some of their billions of dollars of profits at researchers to 'prove' it. Or do they know full-well that it is baloney?

Then again, if you are making that many billions why would you care about anything!

PET Studies show low and transient D2 binding (12-16) and minimal effect on prolactin.
The number of publications doubting the efficacy of quetiapine is small: here is one which is a bit feeble, and does not even mention histamine (17): ~~https://www.nps.org.au/australian-prescriber/articles/concerns-about-quetiapine-3#r4~~

'Evidence' from clinical trials

Antagonism of H1 receptors improves appetite, sleep and anxiety. In the frequently used Montgomery-Asberg depression rating scale***, appetite, sleep, anxiety, and concentration (often impaired due to anxiety) each rate up to a max of 6 points (severe) out of a total of ten items (i.e. max total score id 60 pts). Thus, they make up 24 pts. out of the total of 60. The Hamilton scale is little different.
*** Another example of a shit rating scale: it has almost no rating of the core symptoms relating to psychomotor retardation like drive, energy, motivation, interest; nor of anhedonia, enjoyment, pleasure, satisfaction. So it is rating anxiety more than biological depression.
The claimed improvements from quetiapine (11 papers in a recent 'meta-analysis', all drug-company sponsored (18), see also (19-21)) average only 4-5 pts ***. A child from the bottom of the maths class can figure out that easily adds up to 5-10 points, just from sedative effects. Not rocket science is it!
*** Incidentally, the usual variations of 'inter-rater reliability' (i.e. how different the scores will be if 2 raters asses the same patient) is of that order, viz. ~ 5 pts. I very much doubt if any of those trials tested their inter-rater reliability. Such points help one to appreciate that the scientific standard of these trials is extremely poor.
Look at the scale for yourself: https://psychology-tools.com/montgomery-asberg-depression-rating-scale/ see how small the changes in appetite, sleep, anxiety and concentration need to be to produce this small degree of improvement.
It should also be noted that most of the studies on schizophrenia emanate from China. The evidence of fraud and bias is even worse for Chinese studies than others (22, 23)
And that is called evidence.
These improvements are most convincingly explained by its sedative antihistamine property which is substantiated by the fact that the improvement is manifest in less than one week, and at low doses (< 50 mg daily). Such doses can only be effecting H1 receptors (thus producing sedative, anxiolytic and sleep promoting changes), **at those doses there would be absolutely no effect on D2 (or any other) receptors**. A recent large study of 1,000 patients showed most managed to take it for less than 3 months and only at a dose of 25 – 40 mg a day (21, 24), and the prominent effects were, wait for it, you guessed, yes, tiredness and sleepiness!

As far as schizophrenia is concerned the latest summary from the Cochrane review is: 'Most data that have been reported within existing comparisons are of very limited value because of assumptions and biases within them' (25). And much data emanates from China where fraud and bias is even worse (22, 23). Like I said before, just no good evidence of different or superior effectiveness.

Conclusion

1. No reliable pharmacological data exists that would even suggest quetiapine is likely to be any use for depression except as an anti-histamine and therefore sedative and anxiolytic. But doxepin would be better and 100 x less expensive.
2. No reliable clinical data exists indicating useful superiority for schizophrenia.
3. No reliable clinical data exists indicating usefulness for any form of depression. Quetiapine is an very expensive drug of minimal usefulness. The world would probably be better off without it. I suggest clinicians who 'believe' this works might read the story of Sir Arthur Conan Doyle and the 'Cottingley Fairies'.

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5-HT2A Antagonism

Since there is little evidence that 5-HT2A antagonists directly benefit schizophrenia (65)another possibility is that they could be of some benefit by an indirect influence on dopamine levels in some other area of the brain, like the frontal cortex. There is evidence that 5-HT has a negative feedback influence on various dopamine pathways, including frontal cortical, and that is mediated through various 5-HT receptor sub-types (66). Therefore blocking them removes that inhibition on frontal dopamine levels. However, whether that occurs in those experiencing schizophrenia, and whether that effect is maintained over longer periods of time, and whether that does any good, is a more complex question for which there is little substantive supporting evidence.

And there is more: not only is there is no good evidence that 5-HT2A antagonists directly benefit schizophrenia, neither is there *good* evidence that 5-HT2A agonists cause, precipitate or exacerbate schizophrenia (e.g. LSD). NB **agonist directed trafficking (ADT)** may be relevant here (see refs for explanation and reviews re ADT (67-70), but even 5-HT2A agonists drugs like LSD and bromocriptine, that do (sometimes) cause hallucinations, do not convincingly resemble the hallucinations characteristic of schizophrenia, nor are they major precipitators of schizophrenic syndromes. When I was a young doctor in London great numbers of people were taking LSD on a regular basis and yet I never admitted anybody to hospital who I thought had schizophrenia but who turned out to have taken LSD.

If you wish to read a more optimistic view of the hallucinogen model of psychosis in relation to serotonin and schizophrenia then see Geyer (71). However, in my view Geyer seems to see form and substance where there are only shadows: for instance, the 3rd person auditory hallucinations of schizophrenia are as different as chalk is from cheese compared to the visual hallucinations characteristic of LSD etc. To equate the two is like regarding all forms of chest pain as heart attacks.

We need to remind ourselves that many drugs of abuse like amphetamines, ecstasy (MDMA), LSD and others have all been stated to cause symptoms that emulate schizophrenia. Researchers in their eagerness to bolster the validity of biochemical models of schizophrenia have made all sorts of analogies. Since the above drugs have disparate mechanisms of action, and on different pathways in the brain, it is unlikely that such analogies explain anything much. It is noteworthy that no individual drug from the above list stands out as being more likely to be implicated in the generation of schizophrenia-like symptoms or syndromes. It therefore seems that such ideas have little heuristic validity or explanatory or predictive power (72-76).

Critique of Meltzer: 5-HT2A/D2 Ratio

The most prominent recent review (2011) on this topic "The role of serotonin receptors in the action of atypical antipsychotic drugs" (4) is by Meltzer, the doyen of SGA theorizers and commentators, he concludes:

"The evidence discussed here … **strongly** suggests that more potent 5-HT2A receptor inverse agonist and weak D2/D3 antagonist actions of many atypical APDs are the key determinants of their efficacy and tolerability in schizophrenia."

It may seem audacious to criticize an eminent professor for whom this subject appears to be his life's work: see

~~https://medschool.vanderbilt.edu/psychiatry/faculty/primary/meltzehy~~

&

http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=pubmed&term=Vanderbilt%20AND%20Meltzer%20HY

However, readers may judge for themselves.

Generally: Meltzer's paper (4) concerns animal models of particular aspects of schizophrenic symptoms (rats with schizophrenia has always been a dubious and tortured analogy that has not borne much fruit, see Feifel (77)) and the argument depends on assumptions that known mechanisms of these drugs' actions are their only mechanisms of action, which is unlikely (never mind any metabolites). There are uncertainties and dubious analogies that make this notion unconvincing, as well as apparent "cherry-picking" of data.

For example, it seems perverse to omit the very FGAs that might contradict the hypothesis. Chlorprothixene and chlorpromazine are probably more potent 5HT-2A antagonists than some SGAs, including clozapine, the proto-typical atypical. Note that I say "probably" because receptor affinity data is not necessarily sufficiently accurate to make confident pronouncements about the relative potency of drugs, and furthermore, as alluded to above, the uncertainties relating to the downstream effect of drugs, including agonist directed trafficking, introduce yet further uncertainties (affinity does not always equate with efficacy for a multitude of reasons).

Even if all other technical and scientific aspects of the paper are sound it remains a speculative and poorly supported thesis.

First, it will be obvious, from the agreed lack of superiority of efficacy of the SGAs, that Meltzer's argument contains a major fallacy because it assumes that there is a general superiority of efficacy of SGAs. That superiority is unproven, indeed the evidence is so weak it is still under dispute after years of research: so any consequent deductions are but speculations.

Second, consider this quote, from Meltzer's paper (4), "A **recent** PET study found that antipsychotic drug-naive first epidsode [sic] schizophrenia patients have decreased binding potential for 5-HT2A receptors in frontal cortex (78)." That reference (78) is one of his own papers from 20 years ago. "Recent", 20 years ago? I think not. PET studies were in their infancy then and have advanced a lot

since, see (79, 80). Even if one knew nothing about this subject one should be suspicious of a statement that quotes a 20 year old reference with no more recent studies to substantiate it.

Error Ranges

Third, the data presented in the Meltzer's paper (4) concerning the ratio of D2 and 5-HT2A receptor activities (see also (81)) of these drugs simply does not take into account the inaccuracies and uncertainties inherent in estimating these properties (80, 82). A brief glance at my commentary on interpreting receptor affinity data will make this clear [link]. In Meltzer's table 1 (& Fig 1) the quoted values for receptor affinities have no error ranges and are given to a spurious degree of accuracy. Also, there are no clear references cited, nor any discussion of the choice of values (it looks like the data comes from an old 1999 paper (83)). Why is there no more recent data he can adduce to support his case? In a rapidly advancing field such as this an absence of more recent data over the last 12 years makes me very sceptical.

NB The paper by Richtand et al (81) has much more recent and better receptor data (taken, appropriately, from the PDSP database) and shows very weak correlations which do not look at all convincing. However, they still omit various APs (FGAs)

like: amoxapine, droperidol, flupenthixol, fluspirilene, perphenazine, prochlorpera zine, which are probably significant 5-HT2A antagonists. They make a bewildering number of permutations and combinations of comparisons, e.g. in Table 4:- 5-HT2A/D2, 5-HT2C/D2, 5-HT2A/D3, 5-HT2C/D3, 5-HT2A/D4, 5-HT2C/D4, 5-HT2A * D2, 5-HT2C * D2, D2 (5-HT2A/5-HT1A), D2 (5-HT2C/5-HT1A), D2 (5-HT1A/5-HT2A), D2 (5-HT1A/5-HT2C). None of these produce substantial correlations.

Let us look at his values for olanzapine to start with: Meltzer's table 1 gives the pK_is (log reciprocal of K_i) as, Olanzapine D2 8 and 5-HT2A 8.4, giving a D2/5-HT2Aselectivityratio of 0.4. Skipping over the mathematical errors, like 8 & 8.4 or should it be 8.00 and 8.40, or what? Let us proceed to the choice of these values.

The definitive database for K_i values is the PDSP database which provides the range of HCR values for olanzapine for D2 affinity from 3 to 100 and for 5-HT2A, 2 up to 24. It is quite obvious that if we use various combinations from this range to create a ratio we will obtain ratios that might differ by an order of magnitude from the values given in Meltzer's table (the old data from 1999 that he seems to be using are from rats, but that is not inherently more accurate than human HCR data, so my point is valid). The figure 1 in his paper then plots these ratios as a graph to produce a straight line relating the values on the two axes. However, since the ratios he obtains are seemingly arbitrarily chosen values from arbitrarily chosen drugs (11 out of 19 drugs used are not even established APs), and without

error margins, the values cannot be construed to demonstrate a convincing relationship. The exercise looks like an artifice. For those interested, and have access to Meltzer's paper I will particularise my criticism. The figure on page 61 covers a range of ratios of approximately 1,000 million fold. The only part of the graph that I think is relevant from the point of view of therapeutic drugs is the small oblong group of dots in the middle which cover the range 0.1 to 10. On a log scale that is a huge difference in the ratios. What this means is that the effect of the drug in the living animal or human is highly likely to be completely irrelevant. The concentration range within which drugs have relevant effects is relatively small and drugs that have a ratio of two effects that is much greater than 100/1 will almost certainly have effects which are either too small to be noticeable, or so great that they are toxic. The small number of outliers right and left hand side of the graph are obviously what enables a moderately straight-line to be drawn. However, I would contend that the only relevant section of the graph is a small centre section, and it would obviously be possible to draw a line in virtually any orientation through that group of points. If it were possible to add in a highly relevant drugs mentioned above, like chlorpromazine and chlorprothixine, then I suspect the graph would be meaningless.

1. Meltzer's paper gives as conflicts of interest "HYM is a shareholder and consultant of ACADIA that is developing ACP-103 for Parkinson's Disease. … has been a consultant or grantee of Azur, BioLineRx, Cephalon, Cypress, Dainippon Sumitomo, Eli Lilly, EnVivo, Janssen, Merck, Novartis Pfizer, Roche, and Teva."
   That is a lot of potential conflict.

Postscript: Caveat Lector

When I asked the editor of the journal to publish a comment pointing out problems in Meltzer's paper he stated "I'm not aware that the Current Opinion journals have a precedence of allowing such discussion/comment of papers as you suggest." To which there was only one reply I could give, "Oh- so it not really a scientific journal then." Perhaps they could re-name it "Current One-Sided Opinion". It is, of course, a basic principle of science that comment and criticism of published work must be allowed. Post-publication comment by other researchers is at least as important as pre-publication peer review. Science is not like a papal edict, however eminent professors may think they are (cf. Prof Biederman, below, who equates himself with God).

Remember, always: caveat lector (reader, beware!).

Conclusion: 5-HT2A Receptors and Schizophrenia, Flogging a Dead Horse

Before coming to a conclusion about 5-HT2A receptors and schizophrenia it is useful to step back and remind ourselves again that many drugs, including many FGAs, possess clinically relevant 5-HT2A receptor affinity in humans and have been in use for over half a century. All the following drugs have 5-HT2A K_i values more potent than quetiapine and several other
"SGAs": amoxapine, chlorpromazine, chlorprothixene, droperidol, flupenthixol, fluphenazine, fluspirilene, perphenazine, prochlorperazine, thioridazine, thiothixene, trifluoperazine (data from PDSP data base).
Two specific examples, **chlorpromazine CPZ** (Ki 2-5 nM), chlorprothixene (Ki 0.4-2.0): more potent than many SGAs! All of these are relevant to my area of expertise, serotonin toxicity, because they are such potent 5-HT2A antagonists that they effectively block ST, both in rats and in humans. So they definitely have relevant clinical activity in the usual doses (PET studies support that too (84)). It should be immediately obvious that if 5-HT2A receptor activity was implicated in schizophrenia then CPZ and chlorprothixene would be perceptibly superior to haloperidol. They do not appear to be, and if they are (but nobody claims to have noticed that in 40 years) then they are a lot less expensive than olanzapine, quetiapine etc!
It appears reasonable to leave this discussion by noting another 2011 review "Serotonin 2A receptor antagonists for treatment of schizophrenia", which, hardly surprisingly, concludes, "Three previous 5-HT(2A) receptor antagonists have been discontinued after Phase II or III trials, and available Phase IIa data on the remaining 5-HT(2A) receptor antagonist will need **substantial additional validation** to be approved as a new treatment strategy against schizophrenia." (65).
Has Professor Meltzer spent a long time flogging a dead horse? His paper is not, by any stretch of the imagination, "substantial additional validation".

Quetiapine: Similar Profile to Promethazine and Promazine

We did suggest before that Alice might say, "this is getting sillier and sillier". On the basis of its pharmacological profile quetiapine qualifies as a moderately selective anti-histamine, rather than an anti-psychotic, and is similar, both structurally and pharmacologically, to promethazine and promazine and loxapine. The fact that it has few and weak actions is verified by its toxicity profile which mirrors its receptor profile as a weak anti-histamine with anti-muscarinic effects, the main effects in OD being sedation and delirium (85, 86). Indeed, we could be in Paris in the 1940s (87, 88): I refer to the history of the discovery of the clinical uses of CPZ by Laborit (89). Note that for all three drugs both their receptor

profile, ring structure and 3D configuration are similar.
See http://www.drugbank.ca/
See also newer commentary (2017) specifically about quetiapine http://www.psychotropical.com/quetiapine-the-miracle-of-seroquel
There does appear to be good evidence quetiapine is an NRI via its metabolite N-desalkylquetiapine (aka norquetiapine) (90). That data is from Brian Roth's lab, he runs the PDSP database, so he knows what he is doing. See also (91), which suggests NET occupancy in primates of only 35% with 300 mg/d quetiapine XR. That suggests insufficient potency to produce any clinical effect. There are no other replications of this result, but the Roth value is a Ki of 12 nM. For approximate comparison reboxetine and nortriptyline are ~ 10 nM and desipramine is ~ 1 nM. I have not found any data to indicate if the desalkylquetiapine plasma levels are usually sufficiently high to make it likely that it is routinely acting as an NRI, but that seems unlikely on the current evidence.
This will be discussed in more detail in a future note.
As one who strongly supports the use of Bayesian reasoning, it has to be said that the strongest conclusion that can be drawn from this data is that the clinical trial process itself is flawed (which is hardly news). In other words, if someone can introduce a drug like quetiapine, that is essentially an antihistamine, and convince medical science is an antipsychotic, then drug trials are probably fallible. I doubt if it has any significant effect other than as an anti-histamine and I would like to see some direct comparisons between it and promazine and promethazine. Talk about "the wheel is come full circle" (Edmund, King Lear).
It is difficult to resist pointing out one further major flaw in this "atypical" line of thinking. There are substantial differences (like orders of magnitude) with most of these drugs between their potency for antagonism of numerous receptors, especially dopamine D2 receptors and 5-HT2A receptors. If only partial blockade of dopamine receptors is part of the secret then many of these drugs are going to exhibit too little/great an effect at 5-HT2A or D2 receptors (also, a therapeutic window has been proposed (63) suggesting the optimal level of blockade at 5HT-2A receptors is 60 to 70%). Quetiapine (Seroquel) is such a weak dopamine antagonist (K_i nM D2=500, 5-HT2A=100, H1=7) that it only blocks dopamine receptors to a maximum of 60% at usual doses (usual maximum dose is cited as < 800 mg/day) (92) and then not for long since its half-life is only around 6 hrs! (but it is about **fifty times more potent at H1** receptors, which it swamps at that dose, hence the weight gain and sedation!). For most of the 24 hrs blockade at D2 is minimal, closer to 20%. It is difficult to imagine that has much effect on anything (even in overdose it shows no DA antagonism effects!).
It is also interesting that there are few reliably documented cases of typical NMS with quetiapine (and, of course, the same is true of promazine and promethazine), some are doubtful and/or in the presence of gross brain damage: it certainly

appears it might be less common than with other FGAs or SGAs. That is further evidence it does very little at all except block H1 receptors.
And the problem with getting the right balance of potency at the two receptors at the same time is very much like the difficulty that exists with so-called dual action antidepressants. Most of them have too great a discrepancy in their potency for the two effects (SRI vs. NRI) to be useful. The same argument would appear to apply to SGAs, even if you do believe in the benefit of blocking 2A receptors.
We seem to be besieged by "ifs and buts".

Table of Affinities (Ki nM)

Quetiapine	D2=500,	5HT2A=700,	H1=20
NorQuetiapine	D2=450,	5HT2A=80,	H1=3
Promethazine	D2=250,	5HT2A=170,	H1=1
Promazine	D2=200,	5HT2A=15,	H1=2

Data, as always, from the PDSP database (approximate means from several sources, not all HCR data). Usual error ranges for such assays indicate these three drugs have the same pharmacological profile are likely to be clinically indistinguishable.
Note also that both their ring structure and 3D appearance (configuration) are very similar indeed. See http://www.drugbank.ca/

Agonist-Directed Trafficking

Also, I find it interesting that Meltzer has apparently omitted to address the question of agonist directing trafficking at the 5-HT2-receptors, see (67, 93, 94). More on this another time.

Dopamine Dysregulation

I am not surprised to see this phrase being invoked. If anybody thinks they really know what it means please let me know, but you will probably locate the end of a rainbow first. I recommend reading Sulzer's paper re this (95).

Longer Term Side Effects: the Need for Post-Marketing Surveillance

This commentary is not an analysis of the long-term side effects of these drugs, nor their toxicity in overdose. However, since it appears they are being marketed at least partly on the basis that they are less likely to give rise to legal actions for tardive dyskinesia in the future a few words may be appropriate.

There is no sound basis in theory (except lower equivalent dose) why these drugs should cause less tardive dyskinesia. Even if they do, which must be considered doubtful, this is probably offset by considerations related to metabolic syndrome with its concomitant life shortening complications (96-98).
The proposition that these drugs are going to turn out to have less long-term side-effects is without sound theoretical foundation or evidential basis: it represents a triumph of hope over experience.
Estimating uncommon side-effects and complications resulting from long-term treatment is fraught with methodological difficulties and pitfalls which have clearly not been overcome, as evidenced by the recent analysis of the incidence of NMS (neuroleptic malignant syndrome) by Gurrera (99).
Similar difficulties and pitfalls arise when trying to estimate the long-term incidence of tardive dyskinesia and it seems highly unlikely that any of the figures currently available, or likely to be available for the next decade or two, will be anything like accurate enough to allow comparisons of the relative risk between drugs.
These drugs illustrate in the most dramatic way possible with the awful gap between FDA approval and the establishment of long-term effect. There is not even the shadow of a proper system of post-marketing surveillance in any Western country. This means that reliable data on the longer term effect of these drugs is simply non-existent. About the only data are available in this category comes from socialist Scandinavian countries where they can establish things like eventual suicide and mortality rates with different drugs with at least some degree of reliability cf (6).
We thus have an extraordinary and largely unacknowledged scandal where chronically ill patients are acting as guinea pigs for an unregulated experiment on an unprecedented scale. This applies even more poignantly to the scandalous overuse of these drugs in depressive disorders and other off label conditions. What makes it even more pathetically incompetent and unethical is that no attempt is being made to gather the data that is accumulating as a result of this experiment. It is appropriate to illustrate that statement with a simple example. Many of these drugs cause substantial weight gain, a problem that has profound long-term health consequences. Few doctors possess accurate scales to weigh patients, and even fewer record regular measurements of weight. No central agency collates data, nor is there large-scale aggregation of data, and therefore no reliable scientific statements can be made about the propensity of these drugs can cause weight gain. It is incompetent lunacy.

The Trillion Dollar Cost

The dollar value of these so-called “atypical” antipsychotic drugs is way beyond the financial imagination of most of us. The Eli Lilly drug Zyprexa (olanzapine) has been earning the company 5,000 million (yes, that is 5 billion) dollars per year

for at least the last five years. That represents a substantial portion of Eli Lilly's total sales revenue (5 out of a total of 21 billion). It is understandable that they would be keen to extend their patent and maintain that income stream.

Eli Lilly Company Report

In their 2010 Annual Eli Lilly Company Report, re Zyprexa (olanzapine) the Company state, concerning penalties imposed on them:

"Since June 2005, we have settled approximately 32,720 claims. The two primary settlements were as follows:

In 2005, we settled and paid more than 8,000 claims for approximately $700 million.In 2007, we settled and paid more than 18,000 claims for approximately $500 million.

In January 2009, we reached resolution with the Office of the U.S. Attorney for the Eastern District of Pennsylvania (EDPA), and the State Medicaid Fraud Control Units of 36 states and the District of Columbia, of an investigation related to our U.S. marketing and promotional practices with respect to Zyprexa. As part of the resolution, we pled guilty to one misdemeanor violation of the Food, Drug, and Cosmetic Act for the off-label promotion of Zyprexa in elderly populations as treatment for dementia, including Alzheimer's dementia, between September 1999 and March 2001. We recorded a charge of $1.42 billion for this matter in the third quarter of 2008 and paid substantially all of this amount in 2009. As part of the settlement, we have entered into a corporate integrity agreement with the Office of Inspector General (OIG) of the U.S. Department of Health and Human Services (HHS), which requires us to maintain our compliance program and to undertake a set of defined corporate integrity obligations for five years. The agreement also provides for an independent third-party review organization to assess and report on the company's systems, processes, policies, procedures, and practices. In October 2008, we reached a settlement with 32 states and the District of Columbia related to a multistate investigation brought under various state consumer protection laws. While there was no finding that we violated any provision of the state laws under which the investigations were conducted, we paid $62.0 million and agreed to undertake certain commitments regarding Zyprexa for a period of six years, through consent decrees filed with the settling states."

Gosh! What jolly good chaps they are, so generous and public spirited! Nothing was any fault of theirs, of course! The corporate entity has no memory, its behaviour is psychopathy distilled to the purest essence.

Jansen and Risperdal and Many Others

Jansen make Risperdal (risperidone) which is son of haloperidol, one of the original drugs from the 1960s. That drug alone has earned them around $US 34

billion in total: they are currently (Jan 2012) being sued for 1 billion by the Texas authorities for varies alleged infringements. But they only paid 160 million, the stockholders are happy, and so it goes on and on and …
Google it, you will be busy for days. Almost all major companies have been fined huge sums for fraud. I think Pfizer's 2.3 billion in 2009 is the single largest fine in US corporate history so far, but I doubt that record will stand for long. See e.g. ~~http://temp.fraudpiorg.officelive.com/jjmarketing.aspx~~
Published payments to Doctors in the USA to promote drugs totalled $200 million in 2009. Risperdal's star **Key Opinion Leader (KOL**) (Prof Biederman of Harvard, $1.6 million in payments) when asked on oath in court if there was anyone above his "rank" of "full professor" answered "God". We could go on and on, but do you need to know any more? I do not.

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