1: The Dilemma of Insomnia

At the tender age of seventy, I have always considered myself blessed by the capacity to get a good night’s sleep and watch those wretched ones who claim regular sleeplessness struggle with an existence of baleful misery. Many less fortunate people spend years at a time claiming they have had little or no sleep, feeling tired and depleted all day long and suffering long nights of unremitting despair as they fail to find the off switch to give their exhausted brain release and their bodies a chance to repair their worn out metabolisms and conserve their frazzled telomeres.

Sleep is a complex process, or rather a complex collection of processes. Early in the night we descend in stages to deep slow wave delta sleep that is believed to be essential for restoring the brain’s vitality of function in the day and also for maintaining the body’s own genetic repair and immune systems, reflected in the dynamics of histamine neurons whose oscillations closely reflect the slow delta rhythms.

The complete loss of deep sleep can be lethal. For the 100 or so individuals worldwide who inherit an unusual prion mutation and suffer fatal familial insomnia, the complete lack of being able to enter sleep due to the loss of critical neurons in the basal brain leads within months to death, as the brain sinks into a permanent pre-sleep catatonia and the body atrophies, deprived of its restorative cycle.

That said, as people grow older their amount of deep delta sleep can become briefer and briefer, so that people over 65 may actually have little evidence of the deepest levels of sleep in their EEG.

At the other extreme are the phases of rapid eye movement or REM sleep which is usually associated with dreaming and nightmares, where the brain’s EEG is similar to active waking, but the body is paralysed from the neck down by cholinergic pathways in the basal brain that leave only the eye movements telling the tale of our strange interminable adventures in the world of dreams.

The role of dreaming sleep remains paradoxical. A collection of theories of REM and non-REM sleep have attempted to associate dreaming phases with memory consolidation processes, but these remain speculative and not fully consistent. Studies show that people perform better at memorization tasks when they have had a good episode of REM sleep, however, although we often forget our dreams consistent with memory reprocessing taking place, if we are awakened immediately from REM sleep, or our sleep is disturbed, we can often remember complex dreams in their entirety, or even become aware enough to realize we are dreaming and enter a lucid dreaming state.
The idea that deep sleep is essential is also challenged by wide variations in the sleep needed between species. For example a giraffe only sleeps an average of 1.9 hours, while a tiger slumbers for 15.5 and an armadillo 20.4. This has led to the idea that animals with a high metabolic rate for their body size sleep longer to conserve energy. Sleep periods, which extend to both the vertebrates and arthropods, can also provide a protective role, keeping animals, which are either nocturnal or diurnal, out of the sight of predators during their inactive hours. The extent of the REM phase also varies widely between mammal species. Once evolutionary relationships are factored in, the evidence shows that animals with big brains for their body size need a significantly higher percentage of REM sleep, supporting a role in intelligence and cognitive function (Sleep Medicine Reviews Doi: 10.1016/j.smrv.2007.10.003).

As of mid 2016, a key study has established that sleep, particularly deep sleep, enables synapses to reduce their size (and hence strength) by around 18%, enabling new memories to become consolidated without over-stimulation. This required a four-year double-blind investigation dissecting mouse cortex to establish a general trend over many thousands of synapses. It is consistent with the brain being less electrically responsive at the start of the day and sleep deprivation leading to epilepsy (and ultimately death in the case of rodents) and with the loss of functional capacity on sleep deprivation (Wilson C 2016 *Mystery of what sleep does to our brains may finally be solved* New Scientist 12 July).

People with changing hours, such as shift workers, experience significant cognitive and health deficits as a result. Self-reported short sleep duration (defined in most studies as ≤ 6h) is associated with negative health outcomes: all-cause mortality, obesity, diabetes, cardio-vascular disease, and impaired vigilance and cognition. Biological processes affected in a 2013 sleep study included chromatin modification, gene-expression regulation, macro-molecular metabolism, and inflammatory, immune and stress responses (PNAS doi/10.1073/pnas.1217154110). It is also associated with shortened telomere length and hence ageing (PLOSOne 2012 7/10 e47292 Doi: 10.1371/journal.pone.0047292). In another study, men sleeping sleep 4.5 hours or less or women 3.5 or less inherited a 15% increase in mortality risk, while those sleeping more than 8.5 hours or more also had a 15% increase in mortality (Arch. Gen. Psychiatry 59(2) 131-6. doi:10.1001/archpsyc.59.2.131). Most of the increase was discounted after controlling for co-morbid disorders and the use of sleeping pills, which also increase mortality due partly to overdoses and falls (Pharmacoepidemiology and Drug Safety 2009 18 93-103).

Insomnia is a plague of modern society. People have to struggle with it to maintain stressful careers, or to commute long distances, cope with changing shift work hours, and suffer jet lag on intercontinental flights. Among the many tribulations of pain and anxiety, few are more devastating and maddening than the accumulated fatigue and despondency of several nights of sleep deprivation. People suffer a variety of forms of insomnia from a variety of causes, both psychological and organic from anxiety and depression to hypothyroidism. Some cannot get to sleep. Others wake repeatedly or become wide awake at 4 am and cannot get further rest.

My current encounter with insomnia came like a bolt from the blue amidst an untroubled habit of sleep from around 12.30 to 8.30 or 9 in the morning. I am a pretty speedy alert person and a bit of a night owl as many people are, with a circadian rhythm of slightly more than 24 hours. A few times in the midst of this because of worry about a family member, I woke up at 4 am and couldn’t get back to sleep. Generally the next night I would crash into compensatory sleep, but this time I remained wide awake feeling more awake the more I tried to relax and go to sleep. The third night was even worse. By now I was seriously sleep deprived and caught in one of those cycles where I am so tired I can’t get to sleep for the buzz in my head.

This began to become a pernicious pattern. If I managed to get one good night’s sleep, I could be pretty sure that the next night or two I would lie awake. The more I tried to relax the more I would descend into a maddening deep meditation in which I was fully relaxed but the one-pointed concentration on relaxing was the exact opposite of sleep, leaving my tired brain caught permanently on overdrive. The sheer vigilance required to cope through a long day of brain fatigue even though one’s body has been rested leads to a kind of poisoning so that when you try to sleep your vigilance circuits are over activated and nothing seems to do any good. I tried going for long walks up the nearby mountain in the middle of the night to try to wear my body down into a restful state. For nights on end I could swear I had had no sleep at all. Finally in desperation I negotiated a three or four hour sleep by cadging a sleeping tablet off a family member and at least got a from dawn and felt somewhat revived.
The same day I went to my GP who prescribed melatonin which is often used for jet lag to try to reset by circadian clock and gave me on request a minimal seven doses of temazepam when I deferred the suggestion of the Z-drug zopiclone because it is carcinogenic and causes metal taste.

For the next two weeks I continued to sleep atrociously, occasionally getting a normal sleep if I could actually get off to sleep, but the rest of the time, despite noting the transient dreaminess of melatonin, lying awake most of the night punctuated by short periods of perhaps fours hours sleep towards morning if I took half, or a whole sleeping tablet.
I have a constitutional loathing of stoppers and tranquillizers generally and know they are both habit forming, and have withdrawal symptoms from rebound insomnia to seizures. Although they do give something resembling sleep, it is more a kind of glass box hibernation than actual sleep and can leave one hung over, feeling shaky next day if they are taken too late. That said, sleep deprivation is a serious condition leading to reduced cognitive function, lowered resistance to infection and the onset of diabetes and heart problems. Zopiclone seems to be a little better tolerated, making me feel if anything a little too wide awake next morning, but both drug types have similar dependence and withdrawal profiles, acting in similar ways on GABA receptors and Z-drugs like zopiclone reduce immunity and increase cancer risks.

At the end of two weeks of this, having judiciously only consumed half of the sleeping tablets I had been given, I returned to my GP to say the melatonin had done little or nothing, but I was getting some help from the temazepam. I was both still sleep deprived and feeling shaky for the half temazepam I had taken at 4 am the night before and my demeanour seemed to make her think I was somewhat unhinged. At this point she pre-emptively asserted that I wasn’t getting any more sleeping tablets and that if I didn’t like it I could find another doctor. This wasn’t just any GP, but our family doctor over 35 years, who knew I had never abused sedatives and indeed had sailed through to the age of seventy with almost no medical consultations of any kind. I was aghast and said so. After a near stand up confrontation when she told me that, if seven sleeping tablets didn’t fix it, it would be standard for their practice to put me on low dose tricyclic antidepressants, she reluctantly agreed to give me a further 20 temazepam, provided I set up a monitoring regime with my partner to use them only sparingly.

This is a far cry from the medical profession’s profilageto use of benzodiazepenes when they were first marketed as a magic bullet for tension and sleeplessness in the 1970s and 1980s. Just as the 1990s saw the Prozac age of antidepressive fashion, as if for the first time in world history, large sections of the population were finding the trials of life too melancholy to bear, so the 1970s saw drug companies and the medical profession advancing the idea that benzodiazepenes were the panacea for all the stresses of modern life, used both by executives coping with the high life and as ‘mother’s little helpers’ targeted specifically at vulnerable women coping with the stresses of being stuck at home with screeching babies and mountains of laundry to do. For ten years billions of benzodiazepenes were freely prescribed as an innocuous alternative to the blunt weapon of habituating barbiturates which were far less selective for the GABAa receptors in the brain promoting relaxation and somnolence, before concerns about addiction and withdrawal began to surface. Now the pendulum has shifted so far the other way that agents which do have a legitimate purpose in promoting sleep are avoided by medical professionals like a curse, for fear of patient addiction drug abuse.

To most of us, “tricyclic” is even more of a dirty word, associated with both the worst antipsychotic drugs, which shut down virtually all neurotransmitter systems, turning one onto a zombie on meds and, along with the older heavier antidepressants which turn too many systems on the other way, overall having a spectrum of quite hideous side effects, from tardive dyskinesia, through Parkinsonism to Neuroleptic malignant syndrome. But that isn’t the only concern. If we are sane and not actually depressive, is it right for the medical profession to arbitrarily ascribe insomnia precipitated by genuine life concerns to a psychiatric condition? Do we seriously want to find during an acute bout of insomnia that we are being consigned to long term 24-hours a day medication, which will inevitably alter our innate drug-free consciousness and decision-making?

2: Complementary Solutions to the Problem of Sleep and Ethics of Doctor-Patient Relationships

I will come back to this later but it turns out that the certain tricyclics do have a role in treatment of insomnia because their strongest receptor action is as antihistamines and the low doses used mean that they are predominantly targeting the brain’s histamine H1 receptor, whose activity and inhibition has been discovered to be pivotal in maintaining sleep once it has been initiated.

The history of tricyclics doesn’t just revolve around psychoactive drugs but antihistamines, which those of us who have been around long enough know, were prone to make you drowsy. The original aim of antihistamines was not to act on the brain but to reduce the allergic reactions which are promoted by histamine receptors in the tissues leading to the dilation of blood vessels and filling the tissues with inflammatory interstitial fluid lead to swelling and itching. As time has gone by, newer generations of antihistamines have been devised which don’t cross the blood-brain barrier and hence avoid this drowsiness, but first generation antihistamines such as diphenhydramine (Benadryl) are antagonists for...
the brain’s H1 receptor just as are antidepressants such as doxepin. Unlike the benzodiazepenes and more recent Z-drugs, both of which have problems of habituation and withdrawal, neither doxepin nor doxylamine appear to have significant withdrawal, although their effect may wane in as few as 3 days of repeated use to placebo levels, due to the rapid adaption of the histamine system.

In fig 2 evidence is presented which shows that the use of low dosage antidepressants such as doxepin to treat insomnia, which works principally for sleep maintenance, has a similar effect and no clear advantage over the use of common over the counter antihistamines, such as diphenhydramine and closely related doxylamine succinate, which is in common over the counter medications such as dozile sleep aid in Australasia and with other drugs in Tylenol, Unisom Sleep Tabs, and zzzQuil.

The second point is that the antihistamine agents work in a complementary way to the benzodiazepines and related Z-drugs such as zopiclone, which are GABAA agonists, which promote the onset of sleep by shutting down the arousal system. In fig 3 the basal brain systems supporting alert arousal and sleep onset are illustrated. These form a kind of flip-flop in which the basal GABA system turns off arousal, silencing ascending serotonin, nor-epinephrine and histamine pathways. In turn changes in the firing of the H1 receptor histamine pathway are pivotal in sleep maintenance and in the slow-wave oscillations of deep sleep. The fact that the H1 and GABA systems are independent and complementary means that both drug avenues are valid for addressing insomnia, rather than one replacing the other as prescribing fashion and fear of drug abuse suggest.

Fig 3: Cortical arousal circuits involve a variety of ascending pathways involving histamine, serotonin and nor-epinephrine. Histamine H1 receptors are activated by neurons in the tuberomammillary nucleus of the hypothalamus, which become active during the ‘wake’ cycle, firing at approximately 2 Hz. During slow wave sleep, this firing rate drops to approximately 0.5 Hz. Finally, during REM sleep, histaminergic neurons stop firing altogether. It has been reported that histaminergic neurons have the most wake-selective firing pattern of all known neuronal types. The locus coeruleus is the principal site for nor-epinephrine ascending pathways which maintain vigilance and are almost completely silent in REM sleep. The raphe nuclei send serotonergic projections to wide areas of the cerebral cortex releasing serotonin to the rest of the brain. They also fall silent during REM sleep and are less active during non-REM sleep. They also feedback to the suprachiasmatic nuclei (SCN), providing a responsive basis for circadian rhythms.

The SCN transmits to the raphe nuclei via the dorsomedial hypothalamus nucleus altering serotonin levels for sleep/wake states. The raphe nuclei will then transmit feedback to the SCN about the animal’s vigilance and levels of alertness. The onset of REM and PGO spikes is driven by cholinergic neurons in the pons. Complementing these are GABA projections from the ventrolateral preoptic nucleus VLPO, which inhibit wakefulness and lead to the onset of sleep (CNS Spectrum 2008;13(12) 1047-55). The system is believed to form a flip-flop (right) in which the VLPO shuts down arousal in one phase while orexin ORX neurons promote arousal in the other. Orexin (hypocretin) is produced by the neuronal cluster in the posterior portion of the lateral hypothalamus. Orexin-1 receptors are found in the locus coeruleus, orexin-2 receptors in the TMN, and both types in the median raphe nuclei and mesopontine reticular formation. (Current Neuropsychopharmacology 2008 6 367-78).

Reservations about the pendulum swing from sedative drugs to the widespread use of antidepressants for insomnia is notable in the medical literature.

In Medscape, Thomas Roth notes: Despite the availability of BZRAs and the development of safer compounds within the category [Z-drugs], low-dose sedating antidepressants represent an increasingly used modality for the management of insomnia. Specifically trazodone, and secondarily doxepin, mirtazapine, and amitriptyline, are being used for the treatment of insomnia even in the absence of a depressive disorder. There has been much speculation as to the increased use of these medications for the management of insomnia given that their use for their primary indication, treatment of depression, is
developing research tools that have lasted 1 year or less. A substantial public concern is about the mismatch between treatment options and their benefits. Moreover, even for those treatments that have been systematically evaluated, the panel is concerned about the mismatch between the potential lifelong nature of this illness and the shortest clinical trials, which have lasted 1 year or less. A substantial public and private research effort is warranted, including developing research tools and conducting longitudinal studies of randomized clinical trials. Finally, there is a major need for educational programs directed at physicians, health care providers, and the public (NIH Consens State Sci Statements, 2005 Jun 13-15;22(2):1-30).

Fig 4: The tricyclics were first developed in the 1940s with the antihistamine promethazine. Chlorpromazine, derived from promethazine originally as a sedative, was found to have neuroleptic properties in the early 1950s, and was the first typical antipsychotic. Fluphenazine is a high-potency typical antipsychotic. It is less prone to causing sedation, low blood pressure or anticholinergic effects but is associated with a higher frequency of movement disorders. Imipramine, (fig 2) originally investigated as an antipsychotic, was discovered in the early 1950s, and was the first tricyclic antidepressant, along with amitriptyline the most widely used TCA. Carbamazepine was discovered in 1953, and was subsequently introduced as an anticonvulsant in 1965. Antidepressants with a tetracyclic structure such as mianserin were first developed in the 1970s. Clozapine was introduced as the first atypical antipsychotic in the 1990s, followed by others including Olanzapine and Quetiapine.

When my insomnia began I had a comprehensive series of blood tests to make sure there was no obvious organic cause, such as hypothyroidism. A week later I had a letter from my GP who thanked me for having myself checked out showing a clean slate - heart, blood, thyroid and prostate PSA normal and no diabetes.

Having been plagued by my last medical consultation, not liking the sleep quality and hangover effects of temazepam, I decided to explore whether there were any more natural ways of promoting a good night's sleep than benzodiazepines. After a search through various herbs from Passiflora incarnata, through red ginseng, which is also a stimulant, to Zisiphus and Papaver I settled on Valeriana officinalis as a prospective candidate with some actual scientific evidence for its activity on GABAa receptors.

Valerian, like many herbs, contains a diverse and bewildering array of phytochemicals, but among them are valeroprotiates and valerenic acid, which has been demonstrated in scientific studies to bind to the β2 and β3 components of the GABAa receptor. Although its effects are mild to placebo by comparison with the hammer blow of a good dose of benzos, anecdotal evidence from users suggests they do form a
natural sedative to aid the onset of sleep. In fig 5 is shown the GABA\textsubscript{a} ionotropic receptor, which is a pentamer of individual proteins, combining various \(\alpha, \beta,\) and \(\gamma\) versions to make the active receptor. Binding sites for benzodiazepenes, Z-drugs and the common binding site of valerenic acid and the synthetic sedative loreclezole are illustrated centre.

My insomnia arose from three converging factors: (a) unresolved anxiety about a family member, the precipitating cause, (b) becoming older and needing slightly less sleep and beginning to have intermittent nights when I couldn’t sleep, and (c) my partner also becoming older and disrupting my sleep more with her snuffling and snoring, disrupting sleep onset. With sleep onset insomnia I would literally lie awake all night getting no sleep at all. The ongoing insomnia and the difficulties of seeking appropriate medication then caused months of anxiety and complete uncertainty whether I would be able to get to sleep for nights in a row, so that I would get severely sleep deprived, exacerbating the initial problem.

Recent research into changes in sleep time with age has produced the following trends, which show that contrary to the notion that older people don’t need much sleep, healthy older people sleep nearly as long as young people:

- **Age 20-30:** 433.5 minutes (7.23 hours)
- **Age 40-55:** 409.9 minutes (6.83 hours)
- **Age 66-83:** 390.4 minutes (6.51 hours)

**Effective Strategies:**
Eight months into this situation I have arrived at the following spectrum of responses:

1: **Non-pharmaceutical Measures:** This is the main thrust of my strategy, consistent with cognitive behavioral therapy for insomnia (CBTI).

- **Conducive Setting:** I have set up a spare room where I can go to sleep by myself in an uninterrupted setting in a comfortable bed with covers I can easily adjust for temperature, since hyper-vigilance often causes metabolic over-heating, while natural sleep results in a reduction of body temperature. I have a Nexus tablet with ear buds providing forest insect sounds in an endless two-hour loop (Android AB player), which mesmerizes me, inhibiting cycles of thought and masking background noises. This can frequently get me off to sleep quickly.

- **Reducing Light in the Evening:** The melatonin cycle is driven by light and darkness, so it is important not to expose oneself to intense white or blue light in the evenings. I turn off the bright LED bulbs and use an app for Windows and Mac called f.lux to automatically scale the color tone on the screen.

- **Regular Sleep Timing:** I go to bed at a regular time of 11.30pm-midnight, which is half to one hour after my partner. I avoid looking at the time until I am sure I have already been asleep.

- **Sleep Restriction:** At the same time I try to restrict oversleeping (more than 6.5 hours) by waking up at 6-7 and spending the last hour or so in bed with my partner, to celebrate our togetherness.

- **Relaxation:** After months of insomnia anxiety I have learned to be relaxed and confident about sleeping again. If I can’t sleep for a few hours on occasional nights, I avoid panicking about insomnia and sink to a quiescent state where I have learned again to eventually drift into a few episodes of lucid dreaming towards the end of the night, so that I get at least a couple of hours of brain disengagement.

2: **Natural Supplements:** In the light of the above discussion I arrived at the following natural formulation to aid getting to sleep, designed to use natural alternatives while having some degree of activity on the sleep onset facilitation of GABA\textsubscript{a} agents:

- **1-3 mg melatonin** (to aid sleep onset and reset the circadian rhythm. Higher doses can cause insomnia)
- **50 mg 5-hydroxytryptophan** (the immediate precursor of serotonin).
- **8.4 mg of valerenic acid** (valerian herbal capsules GABA partial agonist)
- **Half a glass of wine** (a small amount of GABA supplementation).
- **0.4-0.7g cannabis butter** 2-4 hrs prior (mild disruption of vigilance 11-hydroxy-THC is soporific)

Having used these for several months I have stopped all but the wine and cbutter, with 1.5 mg melatonin if my sleep becomes irregular, because I am sleeping satisfactorily using the techniques above. However if I run into a period where I am sleep deprived on successive nights, I want the best options medical science can provide. Currently I have a small store of temazepam and doxylamine, which I can use intermittently (currently no more than 1-2 a month each), but if my insomnia became worse I would choose a regime where I have a weekly cycle of the following intermittent type to avoid tolerance to either drug:

- **Mon natural**
- **Tue doxylamine**
- **Wed natural**
- **Thu temazepam**
- **Fri natural**
- **Sat doxylamine**
- **Sun natural**
3: Pharmaceutical Medications: A major part of my confidence about dealing with my insomnia has come from having what I regard as the two best medications medical science can provide, on hand for emergencies, so that if I end up suffering serious sleep deprivation, I can get immediate recovery and regain my health and vitality.

**Temazepam:** After seven months of careful very occasional use I have gained the reluctant assent of my GPs to use temazepam on an intermittent basis of 2 to 3 10 mg tablets a month on well-spaced nights, reassessed each time I ask for a prescription. This low dose intermittent use spaces doses far further apart than could possibly result in any form of tolerance or dependence. I believe temazepam is the best choice of medication because it has optimal sedative properties, few side effects, low toxicity in normal use and a half-life well suited to the duration of recovery sleep without seriously affecting one’s performance the next day.

**Doxylamine:** If I do need to use medications, I try to also intersperse the occasional use of temazepam with alternate use of doxylamine succinate, taken together with the above natural remedies, as a complement to temazepam, superior to a tricyclic as it has no mood and virility compromising side-effects, although like all H1 antagonists, it is for sleep maintenance rather than to put one to sleep, and rapidly declines to placebo after a few nights of continuous use. Its half life (fig 2) is also suited to sleep duration.

4: Rejected alternatives:

**Z-drugs:** I have declined second generation GABA-ergic Z-drugs like zopiclone, which have similar affects to benzodiazepenes and have been touted as safer, because they are now believed to be just as habituating and prone to rebound insomnia as benzodiazepenes and are known to cause a variety of cancers, probably because they inhibit one’s immune system, resulting also in increased susceptibility to infection.

**Tricyclic antidepressants:** I have stringently avoided my GP trying to force me to take doxepin, which, like doxylamine acts as an H1 antagonist, because, even in the lower doses used for insomnia, its serotonin/adrenergic side-effects lead to sexual dysfunction, and obesity. It robs one of one’s autonomy of mood, it doesn’t induce sleep onset and likely reduces to placebo as a sedative after only a few nights, because of the rapid adaption of the H1 receptor system, leaving one on an antipsychotic medication which is ineffective long-term for insomnia. Its biological half life of up to 31 hours (fig 2) extends far into successive days, leading to waking side effects in the day.

![Fig 5: (a) The GABAa ionotropic receptor is a pentamer of five sub-component proteins facilitating Cl⁻ flow. (b) Benzodiazepines such as temazepam bind to the same allosteric modulation site between α1 and γ2 components, enhancing the binding of GABA and thus chloride flow. Z-drugs such as zopiclone bind to the α subunit (J. Pharmacol. Exp. Ther. 317 (1): 369–77. doi:10.1124/jpet.105.096701) with short-acting zaleplon binding selectively to α1. Valerenic acid, in the herbal sleep remedy valerian and the synthetic sedative loreclezole, which again are structurally unrelated, bind to a site on the β2 protein (Neuropharmacology 53 (2007) 178-187, PNAS 91 (1994) 4569-73). This explains why benzodiazepines and Z-drugs show cross-tolerance and both show similar withdrawal effects when used over a period. It is thus likely that valerian will also have a similar tolerance profile with continued use. Valerian extract is also found to be a 5HT5a agonist whose receptors are found in the suprachiasmatic nuclei involved in sleep. Suvorexant is an orexin-1 and -2 antagonist in late phase development for pharmaceutical marketing. The older barbiturates exemplified by Phenobarbital bind to multiple GABA receptor sites but also inhibit excitatory glutamate AMPA receptors adding to their sedative effect and to their danger of lethal overdose.

**GABA-ergic agents versus H1 receptor inhibitors:**
One needs to be cautious about all the sleep medications. All the H1 antagonists also have anticholinergic side effects, including dry mouth, urinary retention, glaucoma and hangover drowsiness. Both benzodiazepenes (and presumably Z-drugs) and the anticholinergics like doxepin and diphenhydramine
have been associated with increases in dementia in people over 65 (BMJ 2014 doi: 10.1136/bmj.g5205, JAMA Intern Med. doi:10.1001/jamainternmed.2014.7663) with over 180 daily doses contributing to an approximately 50% increase, in both classes of sleep medication. Neither of these studies are causally conclusive, but the linkage in at least the anticholinergics has tried to avoid pre-existing dementia being a cause of sleep aid medication. GABA-ergic sedatives are also associated with an increase in mortality due to elderly people suffering fractures resulting from falls in the night, because they impair coordination.

One also needs to understand the differing efficacies and side-effects of the two types of agent. GABAergic benzodiazepines and Z-drugs are the drug of choice, and really the only medication effective at sleep induction because the GABA circuit is key in tipping the see-saw to precipitate sleep onset (see fig 3). H1 antagonists, including doxepin and the antihistamines such as diphenhydramine and doxylamine, aid sleep maintenance but not sleep induction, so they don’t work for people with hypervigilant insomnia. All the GABAergic agents have a tendency towards tolerance, dependence and rebound insomnia, as does alcohol, which in some people can emerge within a week or two, but others appear to be able to use these drugs for years without manifest ill effects, particularly if they space their use so they are taken only one night in three to seven. Tolerance varies both with the specific drug used, and probably with the person’s genetic makeup, but it is also characteristic of GABA receptors themselves. Nevertheless withdrawal can have severe consequences due to cerebral over-excitation, including seizures.

Overall the sleep quality and hangover is drowsy on doxylamine, and it is not effective at sleep initiation, but one has to trade this off against the glassy hibernation sleep of benzodiazepines and Z-drugs, which are known to distort sleep patterns away from deep sleep to stage 2 and to inhibit REM sleep as well (Sleep 2003 26/3 313-7) although many people find they give a refreshing sleep, particularly at the beginning of treatment, in stark contrast to their insomnia.

**Orexin Agents:** A third avenue, involving orexin-1 and -2 receptor antagonism is in various phases of research development, and one product, suvorexant, has been approved by the FDA. However the orexin system is very sensitive to damage as there are only 10,000 to 20,000 orexin neurons in the brain fanning out to form an ascending pathway similar to those of serotonin and nor-epinephrine. Autoimmune destruction of orexin neurons leads to the disabling failure of sleep regulation known as neurolepsy.

**CBTI:** I have judiciously applied techniques of cognitive behavioural therapy for insomnia as noted above, by taking account of the literature, but without needing to go to a $250 a session clinic. ([http://www.mayoclinic.org/diseases-conditions/insomnia/in-depth/insomnia-treatment/art-20046677](http://www.mayoclinic.org/diseases-conditions/insomnia/in-depth/insomnia-treatment/art-20046677)).

**Side Effects and Patient Reviews:**

**Benzodiazepenes:** You can find a definitive manual on benzodiazepenes and their dependence by Prof. Heather Ashton at ([http://www.benzo.org.uk/manual/bzcha01.htm](http://www.benzo.org.uk/manual/bzcha01.htm)) and responsible use of benzodiazepenes by the same expert at ([http://www.benzo.org.uk/asgr.htm](http://www.benzo.org.uk/asgr.htm)). Ideally one should not use them for more than a week or two, use the lowest effective dose and to use them no more than every third day intermediate term, to avoid build up of tolerance. You will also find that they rank highly in statistics of drug abuse because some people find them pleasurable, and nearly as many people die from overdoses as do from opiate drugs as sleeping tablets are favoured choices for suicide attempts.

**Temazepam patient reviews:**

![National Overdose Deaths](image)

<table>
<thead>
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<th>Number of Deaths from Benzodiazepines</th>
<th>Number of Deaths from Rx Opioid Pain Relievers</th>
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<td>Total Female Male</td>
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<td>Gender Distribution</td>
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Sources: National Center for Health Statistics, CDC Wonder.
Temazepam works fantastic for insomnia. If you don’t mind using a prescription medicine, it’s the best for insomnia. No side effects to report, and no next-day drowsiness. I use the lowest dose- 7.5mg, with melatonin, because melatonin is a powerful antioxidant, and I sleep great, feeling refreshed in the morning. I thank God for both temazepam and melatonin.

Worked for the first couple weeks. Now I am up to 60mg just to get to sleep. Its been two hrs and no sleep. Its slowly not working anymore. Been on it for a month.

I have been taking 10 mg per night for 29 years. It relaxes me so I can sleep for 4-5 hrs tops.

By 3rd night of use, it became ineffective. My system built up tolerance quickly. Fourth night I took 40 mgs and only 4 hours of sleep. Dr. just prescribed a months worth. Now I must find an alternative while I ween myself off temazepam. Not easy since I wasn’t getting any sleep at all before I started.

False awakening dreams, nightmares, vivid dreams, reduced effectiveness over time.

This is the best sleeping pill I’ve ever tried. 30 years now, and still no tolerance issues. I wake up refreshed, no hangover, unlike all the other sleeping pills, as temazepam is very mild, yet it keeps you asleep. I take 15 or 30 mg, depending how I feel. I have tried Halcion and Dalmane, which weren’t very effective. I also tried Ambien in the mid 90s and had horrible sleepwalking episodes. This has never happened with Restoril.

I have been taking Temazepam for approximately 20 years with great results. The key is to take it sparingly, and no more than one time per week. I usually take it approximately one time every 10-14 days, and it works wonderfully. I normally go to sleep within 10 minutes and sleep 6-8 hours uninterrupted and wake totally clear headed and no grogginess.

Tricyclics: Doxepin and Amitriptyline are antidepressants altering serotonin and adrenergic metabolism, which have a variety of potentially serious side effects. These include very rapid weight gain, sexual impotence, and movement disorders (hypokinesis), which are notorious with tricyclics, and can lead to potentially irreversible Parkinsons and T ourette’s syndromes. These tend to be ignored by doctors, who prefer them to GABAergic agents because they have little risk to the doctors’ reputations for allowing patient dependence to occur, so some will refuse GABAergic drugs even when they are the indicated drug of choice and try to dish out doxepin long-term. One of the most concerning aspects of this is to be told to take a mood altering drug long-term, which compromises one’s emotional autonomy and psychological decision-making, so you really aren’t quite the same person any more. This is fine if you are depressed and in need of support for one’s mental condition, but is a fundamental invasion of your personal identity otherwise. While doctors originally pushed benzodiazepenes as mother’s little helper, later it has come to be antidepressants that are dished out like lollies, because doctors have little fear of comeback, even if the patient’s life is significantly compromised. Doxepin is another example of medical marketing taking an existing early-generation drug normally prescribed only for more severe cases of depression and pushing it for another condition - insomnia - because it is also a strong antihistamine that crosses the blood brain barrier. The H1-antagonist antidepressants like doxepin are liable to be prescribed long-term as antidepressants usually are, because doctors don’t fear short term dependency or drug abuse, despite the fact that their H1 potency can last as little as three nights, leading to manifest over-prescription.

Although doxepin is not addicting, withdrawal symptoms after abrupt discontinuation may occur and include hypertension, tachycardia, restlessness, abdominal distress and emesis. Withdrawal mania has also been reported (See patient experience later). The 10% rule holds for doxepin: Reduce progressively by 10% per month, calculated on the last dosage – i.e to 90% compounding down monthly.

Doxepin for insomnia patient reviews

Doxepin is great at keeping me asleep. The only major problem is the rapid weight gain. I went from 155lbs to 185lbs in only 2 weeks.

Helped me a lot with my insomnia. But gained over 50 pounds in the last 4 months. I have also noticed my hair getting thinner. I will not take this anymore. Going back to the dr.

This medicine was just like taking Benadryl, only more expensive. An hour to two hours after taking Silenor, I
still couldn't fall asleep...not even the slightest bit tired. Once I had fallen asleep, I would wake up 2-4 hours later and be wide awake for the rest of the night.

Like most medicines, the first few days it worked like a charm. … The bad thing about this medicine is that you feel very sedated throughout the day. You know you slept because of the vivid dreams and you don't wake up the whole night. Nevertheless, you feel extremely tired the whole day. I tried this for two weeks and yet I never got to sleep on it. I had to try it for two weeks because otherwise my doctor wouldn't give me anything else.

I was given doxepin 50mg after a very bad experience using Xanax for insomnia. It works fine for my depression, I have a good energy level during the day, but it doesn't do a thing for my insomnia. I feel that if I can solve my insomnia it would go a long way to helping my depression.

Silenor was a nightmare for me. I stuck with it for about 3 weeks and thought I was going out of my mind. I did not sleep at all for the first 4 days and then the hallucinations began. If I did sleep it was in for about 30 minutes at a time and then the terrible nightmares kept me awake for the rest of the night.

First night on 10mg didn't fall asleep until 5:15 am after 4 am popcorn binge. Woke up about 7:30 am. Same on next 3 nights with middle-of-the night coffee-cake, chocolates and even a couple of frozen dinners. Dr. upped to 20mg. Same result. Hardly any sleep, night snacking, and started eating more during the day. People have commented about rapid weight gain. They're right. I gained 8 lbs. the first week! My weight has been pretty consistent by 2-3 lbs. for years. Going back to Ambien!

I strongly question the use of doxepin, except for people who may have a significant underlying depressive cause of insomnia where the two effects may work synergistically and where early awakening can be a symptom. For a woman to try to cure insomnia and find she has blown up like an obese balloon in front of her husband, or a man in later mid-life who finds that his sexual relationship with his partner is reduced to a fumbling shadow if his former prowess, this is extremely hard to justify, because one's bodily attractiveness and sexual fulfillment are key to feeling one's full vitality and health and for a doctor to compromise these merely to protect their own reputations of avoiding potential drugs of abuse is a violation of medical ethics. To me it is an absolute crime of the medical profession to foist tricyclics, which needlessly compromise an over 65 year oldxs capacity to enjoy a sexually active life conducive to health and wellbeing of both themselves and their partner and experience of intimacy together and the fullness of life in mid-age, simply because they can't trust well-informed patients to take sleep medication intermittently enough to avoid dependency.

The Unseemly Politics of Insomnia Medication

To my absolute dismay, when I wrote to my GP to let them know I had handled their reluctant medication so responsibly that I had used only one from the second prescription in two and a half months, but was still having intermittent trouble for which I considered temazepam to be the appropriate choice, she declined to even consider further medication and tried to palm me off to an expensive private clinic for cognitive behavioural therapy, washing her hands of my medical care in so many words. This to me is a complete violation of medical ethics and shows how far doctors are prepared to go in treating their own imaginary and unjustified concerns, reducing the patient to a mere cipher – a public health drug abuse statistic, failing to treat on the basis of informed consent and reneging about this medicine is that you feel

I was not depressed and did not have an anxiety neurosis, so being told I would get nothing but tricyclic antidepressants after a week in which I used only 3 sleeping tablets was an absolute anathema. I found my GP’s attitude to be completely counterproductive, causing further anxiety and lack of confidence to treat the problem. It is also a failure of medical ethics. A GP visit should be a consultation with a patient to avail them of the possible treatments and their risks and benefits on the basis of informed choice, just as informed consent is required for an operation, not a dictatorial “take it or go somewhere else” edict stipulating a treatment inappropriate for the onset type of insomnia. General caution about potential drugs of abuse should not reduce the doctor-patient relationship to a cipher of public health protocols and potential abuse statistics. Neither should the doctor be treating their own anxieties about drug abuse and their professional reputations, rather than the patient.

In the process I researched all my friends and acquaintances and found many were semi-permanently using Z-drugs. I compiled a short list of other GPs who were prepared to take a more pragmatic view and
prescribe sleep medications when the patient felt they needed them. At the same time I set out to use sleeping tablets so occasionally that I was eventually able to return to my GPs medical practice consult the head practitioner and gain agreement, albeit reluctantly, for another round of temazepam on the basis of six months of extremely impeccable minimal use of only 2 to 3 tablets a month.

The whole basis of modern medicine is patient-specific treatment. Each patient is different genetically and mentally. Some have little knowledge of medicine and need firm guidance, but others need informed choice and the knowledge of being in control of their treatment to conquer the condition, particularly one like acute insomnia, which can be very debilitating to one’s confidence. This is a major ongoing conflict area with psychotropic drugs and pain medications.

3: Drug Marketing Trends and the Over-prescription of Medical Psychoactive Drugs

The 2013 New York Times article “A Glut of Antidepressants” notes a level of antidepressant use in the US particularly in middle aged women echoing the profligate use of “soma” to pacify society in Aldous Huxley’s “Brave New World”: One in 10 Americans now takes an antidepressant medication; among women in their 40s and 50s, the figure is one in four (http://well.blogs.nytimes.com/2013/08/12/a-glut-of-antidepressants/).

Fig 6: Advertisements for antidepressants targeted at women.

Targeting of women for psychoactive medication has a long history. The benzodiazepine tranquilizer Valium was marketed as a “mother's little helper” for women with children experiencing problems of handling their situations. 2.3 billion pills were sold by Roche at Valium’s 1978 peak. They were freely prescribed for 10 years, before their dependency potential became a concern.

Prozac (fluoxetine) made Eli Lilly into a $66 billion dollar company from a $6 billion one.

The nature of gender targeted advertising is exemplified by the three passages aimed at prescribing doctors giving vulnerable women benzodiazepenes:

Her mother’s obvious reference for her older sister has always rankled this patient. The deaths of her father and husband accentuated her alienation and hostility. Hypochondriasis is the way she disowns her conflicts. While you gradually turn her away from somatic concerns and guide her through old hidden problem areas, you can ease her undue psychic tension with valium (diazepam).

Fig 7: Oxazepam advertisement targeting a vulnerable female.
You can’t set her free but you can help her feel less anxious. You know this woman she is anxious, tense, irritable. She has felt this way for months. Beset by seemingly insurmountable problems of raising a young family and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance have helped some but not enough. Serax (oxazepam) cannot change her environment of course, but it can relieve anxiety tension, agitation and irritability, thus strengthening her ability to cope with day to day problems.

M.A. (Fine Arts) … PTA (President-elect) … representations of a life currently centered around home and children, with too little time to pursue a vocation for which she has spent many years in training … a situation that may bespeak continuous frustration and stress a perfect framework for her to translate the functional symptoms of psychic tension into major problems. For this kind of patient – with no demonstrable pathology yet with repeated complaints – consider the distinctive properties of valium (diazepam). Valium possesses a pronounced calming action that usually relieves psychic tension promptly, helping to attenuate the somatic signs and symptoms. Valium is well tolerated. On proper maintenance dosage, valium seldom dulls the senses or interferes with functioning.

The nature of this advertising raises significant social issues. Both tranquilizers and antidepressants are aimed at vulnerable individuals who suffer stress or depression for a variety of reasons. Drug companies advertise because this is expected to increase their sales and profits. There is thus an incentive to seek out vulnerable social targets and advertise in proportion to the potential gains. If the market share for say antidepressants is skewed towards a large number of women in mid life, so the advertising will seek to exploit this market ad create a positive feedback encouraging more people in the identified categories to take up the medication. It is particularly noticeable in this advertising that categories particularly of women are chosen not because of organic physiological problems but real life constraints, such as sacrificing one’s career to raise a young family which are now turned into semi-psychiatric conditions to be treated by drug regimes, putting a clear pressure on the medical profession to misidentify problems requiring family counseling as anxiety neurosis or clinical depression.

Between 2000 and 2011, antidepressant use in Australia increased by 95.3%. In 2011, antidepressants accounted for 66.9% of total psychotropic drug prescription totals, far greater than anxiolytics (11.4%), antipsychotics (7.3%), mood stabilisers (5.8%), sedatives (5.5%), or ADHD medications (3.0%) (Aust N Z J Psychiatry. 2013 Jan;47(1) 74-87. doi: 10.1177/0004867412466595).

A US study, published in April 2013, found that nearly two-thirds of a sample of more than 5,000 patients who had been given a diagnosis of depression within the previous 12 months did not meet the criteria for major depressive episode - the level of depression which is known to be amenable to medication, by contrast with minor or situation caused depression, which is better treated by personal counseling and addressing the actual causative problems. Six out of seven patients, age 65 and older, who had been given a diagnosis of depression did not fit the criteria. The vast majority of individuals diagnosed with depression, rightly or wrongly, were given medication. Most people stay on the drugs, which can have a variety of side effects, for at least two years. Some for a decade or more (Psychotherapy Psychosomatics 2013;82:161-9 Doi:10.1159/000345968).

The OECD report “Health at a glance 2013” notes concerns about appropriateness of antidepressant prescribing: The consumption of antidepressants has also increased significantly in...
most OECD countries since 2000. Guidelines for the pharmaceutical treatment of depression vary across countries, and there is also great variation in prescribing behaviors among general practitioners and psychiatrists in each country. Iceland reported the highest level of consumption of antidepressants in 2011, followed by Australia, Canada, Denmark and Sweden. In 2008, almost 30% of women aged 65 and over had an antidepressant prescription in Iceland, compared with less than 15% in Norway. Greater intensity and duration of treatments are some of the factors explaining the general increase in antidepressant consumption across countries. In Germany there was a rise of 46% between 2007 and 2011, which was less affected by the economic crisis and experienced a more rapid economic recovery. In England, the increase in antidepressant consumption has been associated with a longer duration of drug treatment. In addition, rising consumption levels can also be explained by the extension of the set of indications of some antidepressants to milder forms of depression, generalised anxiety disorders or social phobia. These extensions have raised concerns about appropriateness (http://www.oecd.org/els/health-systems/Health-at-a-Glance-2013.pdf).

Fig 9: Shire a “Global Innovator in Specialty Biopharmaceuticals” whose flagship mission statement reads “To be as Brave as the People we help” offers mixed amphetamine salts for ADHD in the form of adderall-XR. The advert targets girls although ADHD is three times more common in boys.

While antidepressants have little or none of the recreational abuse potential of GABA antagonists such as benzodiazepines, largely because they are not that nice to take, Des Spence notes in the British Medical Journal that they still have profound habituation problems because people fear that discontinuation will result in recurrence of depression: A policy of ever lengthening courses of antidepressants is a product largely of “expert” opinion, not evidence. Before we continue with this policy the psychiatric community must produce evidence of benefit. The internet is awash with harrowing patient stories of side effects such as gastrointestinal disturbances, hypersensitivity, anxiety, insomnia, tremor, hallucinations, drowsiness, sexual dysfunction, hypomania, and suicidal behaviour. Research also suggests that half of patients experience a withdrawal syndrome. Patients are reluctant to stop antidepressants, assuming these symptoms mark a return of their depression. Some even believe they will never feel “happy” without medication (BMJ 2013 346 f191 doi:10.1136/bmj.f191).

There are also notable cases of people finding that they suffer significant withdrawal symptoms from even missing a single day’s dose of some antidepressants such as effexor (venlafaxine fig 2) which seems particularly difficult to taper off from. “In August of 2012, I had 2 days of very scary vertigo type symptoms – that’s what I thought it was. Dizziness, headaches, severe lightheadedness, nausea. When I finally realized (weeks or maybe months later) what it was, it scared me. I had missed ONE day of my Effexor meds.” There is a known strategy to begin taking prozac (fluoxetine) and at the same time taper off effexor over two weeks.

Common withdrawal symptoms for paroxetine one of the more side-effect ridden antidepressants, include nausea, dizziness, lightheadedness and vertigo; insomnia, nightmares and vivid dreams; feelings of electricity in the body, as well as crying and anxiety. “I started to take Seroxat in the Autumn of 1997. My dose was 30mg daily. In May 2004 my Doctor suggested that I reduce that to 20mg daily. Unfortunately I had problems with the reduction to 20mg and things were so terrible I went back up to 30mgs within a week. I felt better as soon as I did this. This was a real shock to me and I started to do a little research on the internet. This was another shock to me - to find a huge community out there who had similar stories to tell... looks like I’ll have to stop it rather than reduce it I decided. Once I took that decision – to stop Seroxat altogether – I thought it would be easy for me – after all, I stopped smoking with little or no fuss. It
took me 22 long months to wean off Seroxat and I suffered many mental and physical terrors and traumas. As I write I’m 10 months off Seroxat and my brain and body are STILL trying to adjust to life without it (https://seroxatsecrets.wordpress.com/about).

Doxepin and related tricyclics can also cause profound withdrawal effects if used long-term. “I have been taking a tricyclic (Doxepin or Amitriptyline) for 13 years for migraine headaches [not for depression]. Now the headaches are gone - but I cannot get off these evil drugs and it is very clear the medical professionals don’t want me to either. I started at 50mg and had gone down to 30mg over time no problem. I hovered at 30 for years because each time I went to 20mg the headaches would come back. Motivated by the risk of long term side effects, I stayed at the 20mg through the headache which lasted 10 days then went away - but I had a new symptom - surges of dizziness. For 2 weeks I was great - the dizziness was there but I felt my mind start to clear. Then with no warning I went down - I thought I was passing out, but then it turned into a seizure, but I was totally coherent just out of control of my jerking body. Then all hell broke lose in the next few days. I had all the flu like, dizziness, electric shock waves from the back of my scull to front, couldn’t eat and if I did it just came right out with the intermittent seizures and now we add anxiety - the kind that grips your very being - makes you grit your teeth and doubt every fiber of your being. In my case I had to go back on the drug and get well and sane again and do it right this time. It has been 4 months since I am back on the 30mgs and I am still not 100% (http://icfda.drugawareness.org/Archives/Survivors/2004/record0040.html).”

The FDA appears to be constitutionally biased towards protecting suspect antidepressants and the pharmaceutical industry, rather then affected patients. “In 2004 for example, a Food and Drug Administration medical officer was told by top agency officials to delete material on the risks of antidepressant drugs from records he was submitting to Congress and then to conceal the deletions, according to documents released yesterday at a hearing on Capitol Hill. The FDA said the deletions were required because agency rules require that ongoing investigations be kept secret. A bipartisan House panel said the FDA also repeatedly prevented Andrew D. Mosholder from disclosing his conclusions that Paxil, Zoloft and Effexor were associated with an increased risk of suicide among children, potentially delaying the issuance of a public warning. The hearing produced new demands from legislators to know why the FDA did not respond sooner to concerns about the widely used antidepressants. Another document released showed that as far back as 1996, an FDA official had suggested an increased risk of suicide among children taking Zoloft. Agency officials repeatedly said that they were worried that the controversy would needlessly frighten parents and families away from useful drugs. Many clinicians believe the drugs are effective against depression. Regulators were at the time weighing whether to add to the labels information about studies that found most of the drugs to be no more effective than sugar pills.” (Vedantam S 2004 FDA Told Its Analyst to Censor Data on Antidepressants Washington Post 24 Sep washingtonpost.com/wp-dyn/articles/A45643-2004Sep23.html).

A Guardian article noting the OECD warning about antidepressants comes with a video with a series of interviews with antidepressant users illustrating that antidepressant use is beneficial only for people with a serious clinical depression episode and leaves many people with minor depression in a permanently drugged state which compromises their mental autonomy and life judgment as well as for many, their enjoyment of life. Also notable is the preparedness of medical practitioners to diagnose serious conditions such as bipolar disorder on assumptions gained from a superficial 10 minute consultation (http://www.theguardian.com/society/2013/nov/20/antidepressant-use-rise-world-oecd).

If one in four women in the US in their 40s and 50s are on semi-permanent psychotherapeutic medication this means that major processes of decision making by women in stressful managerial positions are being affected by a pervasive soma mentality. This presents risks to society at least as significant as misuse of...
recreational drugs.

While concerns may be raised about habituating drugs of potential abuse which also have serious withdrawal symptoms, similar concern has to be raised about institutional use of long-term psychiatric medications on large sections of the population, whose side effects are equally apparent and psychological long-term dependence is manifest in the ever-extending prescription periods of 2 - 10 years and increasing dosages.

In "The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration" (Prevention & Treatment, 5/23 http://alphachoices.com/repository/assets/pdf/EmperorsNewDrugs.pdf), Irving Kirsch, and co-authors make a case that antidepressants have little more than a placebo effect except in the case of severely depressed patients, where the placebo effect is negligible. The case has also been published as a paperback with the same name.

While analyzing antidepressant trials as part of his research into the placebo effect, Kirsch concluded that drug companies do not publish most of their disappointing drug trial results and do publish most favorable results, and that most decisions about the efficacy of a drug are based only on published results. Using the Freedom of Information Act, he and his colleagues acquired from the US Food and Drug Administration the unpublished trial results for six antidepressants. When the results from both published and unpublished studies were averaged, the researchers concluded that the drugs produced a small but clinically meaningless improvement in mood compared with an inert placebo (sugar pill).

To determine whether their averaging of results was hiding a meaningful benefit to more-severely depressed patients by combining their results with those of moderately and mildly depressed patients, he and his colleagues undertook another study, this time of the four new-generation antidepressants for which all trial data were available, and concluded that the difference between drug and placebo effect was greater for more-severely depressed patients, and that this difference was clinically meaningful (but still relatively small) only at the upper end of the very severely depressed category.

Fig 10: Thorazine (chlorpromazine fig 2) is a typical tricyclic antipsychotic used for schizophrenia and bipolar disorder, which shuts down all the neurotransmitter pathways from serotonin, through nor-epinephrine and dopamine to histamine and acetyl-choline. Here the man on the left is clearly portrayed as in a manic and violent state lashing out at imaginary enemies - a classic portrait of paranoid ideation: "Thorazine is especially effective when the psychotic episode is triggered by delusions or hallucinations. At the outset of treatment, Thorazine’s combination of anti-psychotic and sedative effects provides both emotional and physical calming. Assautive or destructive behavior is rapidly controlled". But the woman on the right is simply emotionally upset about menopause, a perfectly reasonable non-psychotic concern. Nevertheless we use an antipsychotic on her: "Thorazine can facilitate the overall management of your menopausal patient. Its unique, non-hypnotic tranquilizing effect relieves anxiety, tension, agitated depression and helps you to restore to the patient a feeling of well-being and a sense of belonging." The same drug that renders the schizophrenic docile cannot restore to the menopausal woman well-being and a sense of belonging. It is clearly a use of marketing to identify vulnerable new targets.

Non-abusing recreational drug users operating in a paradigm of autonomous decision-making choose to
take psychoactive drugs only on an intermittent basis to be high when they are celebrating, while the rest of the time choosing to remain drug free, so that they can make constructive life enhancing decisions in a clear mental state. While one understands that there are situations where a depressed person will seek antidepressant medication, or a manic person may be required to undertake antipsychotic medication, the dependence of the medical profession on regimes of medication taken constantly over months and years represents a significant compromise of patient autonomy and freedom of outlook - a basic human right - in favor of treatment regimes which give the practitioner security of control over the patient’s behavior to minimize risks to the practitioner and their practice. This is a conflict of interest with the patient’s best interests and welfare.

Nowhere is this contrast more stark and striking than in the context of antipsychotic drugs which are prescribed long-term often against a person’s will either in mental institutions or as a condition of release into the wider world to ensure they will remain pacified and non-threatening to others.

As can be seen in figs 2(a), the antipsychotics act as antagonists on almost the whole spectrum of ascending modulatory transmitters that give emotional mood, motivation and decision making their personal characteristics, including the dopamine, serotonin, no-epinephrine, histamine and acetyl-choline pathways, illustrated in fig 11, with a particular emphasis on the dopamine D2 receptor involved in motivation and decision-making. They also have a variety of long-term side effects, including serious movement disorders tardive dyskinesias and Parkinsonism, heart problems, obesity, hypotension, confusion and sedation. By contrast psychedelics act as super-agonists on serotonin receptors, particularly 5HT2a, precipitating a change in the glutamate dynamics through associated metabotropic glutamate receptors.

![Fig 11: Ongoing fast excitatory electrical activity of the brain is mediated through the excitatory neurotransmitter glutamate in feedback with the inhibitory neurotransmitter GABA, or gamma-aminobutyric acid neurons, both driven by ionopore receptors which change the electrical current through ion flow. Five ascending pathways common to mammals arise from the basal brain moderating slow changes in consciousness from sleep to waking and mood and drive, through metabotropic receptors which change activity through protein interactions in the neuron. The five are dopamine (providing drive and decision-making), nor-epinephrine (monitoring vigilance), serotonin (expressing aspects of mood), histamine and acetyl-choline, both acting in complementary ways to maintain alertness. Antipsychotics generally act as antagonists, which dampen the activity in these circuits, leaving the person more docile and less prone to delusion.](image)
unknown, but the first study concludes this upregulation is positively associated with severe dyskinesias. Haloperidol has also been shown to metabolize in the liver into toxic metabolites HPP+ and RHPP+. HPP+ is a structural analog of the more widely known Parkinson’s producing neurotoxin MPP+ and its precursor MPTP. Unlike MPP+, HPP+ is not dependent on monamine oxidase MAO-B for metabolism to toxic species and does not require functional dopamine transporter protein for intracellular uptake. It is toxic to both dopamine and serotonin neurons. A long-term retrospective study found a significant positive correlation between levels of HPP+ and severity of tardive dyskinesia. The receptors 5HT7 and sigma1 are both irreversibly inactivated by haloperidol. Studies showed shrinkage of whole brain by 10% focused on glial cell loss with a 5% drop in neuronal mass.

In a 2013 article in the Telegraph "Why are women still considered more insane than men?" Will Nicoll notes that the new issue of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), which the British Psychological Society fears that the book might medicalise behaviour which is, actually, fairly normal looks set to generate a whole new raft of medical advertisements based on the updated categories of psychiatric illness. Dr Reg Peart, a critic of tranquilizers, noted, that “the level of science in psychiatry lies between astrology and witchcraft”.

Will quotes a study which found that 29 per cent of women, compared to 17 per cent of men are likely to have been treated for a mental-health problem. When depression, alone, is considered, the difference is even more pronounced. NICE the National Institute for Health and Care Excellence found that one in four women will require treatment during their lifetime – compared with only 1 in 10 men despite the fact that there are relatively few reasons to explain the actual scale of the disparity.

Professor Malcolm Lader, Emeritus Professor of Clinical Psychopharmacology at King’s College, London doubts this disparity is justified: “There are special influences operating in women which are absent or less important in men, citing the disorders associated with childbirth, such as puerperal depression and psychosis. But those are, obviously, extreme examples. With respect to conditions such phobias and anxiety disorders the ratios are probably about equal, With the willingness to admit or deny symptoms distorting the figures.” However this distinction is important because many of the drugs used often – namely the SSRI antidepressants – are not only licensed to treat depression, but also a variety of anxiety disorders, which make female patients key consumers.

In an article in MS magazine “Selling Sanity through Gender” (MS Fall 2003 40-45) Jonathan Metzel illustrates how a change of emphasis to slick patient marketing has resulted in patients demanding antidepressant brand names they have seen advertised in the media:

Fig 12: Effexor: Does it take a drug to get mommy back?

Sarah was a 33-year-old publicist and mother of two with what she described as “motherhood problems” “Some days I feel so irritable that it’s hard for me to get out of bed. I know there are things that I should be doing, but I just don’t have the energy” She had stopped making breakfast for her children, a job
now performed by her husband and had fallen behind in what she perceived to be her household duties. She felt her productivity had suffered at work though no one had yet noticed. “I don’t think I’m depressed – in fact my mood has been okay. I just feel overwhelmed by my life”. Rejecting suggestions of psychotherapy or couples counseling she said “You’ve got it all wrong! I don’t have time for therapy. I came to ask for Paxil”. He points out that some doctors, pharmaceutical industry and patients rights advocates argue such advertising has a positive effect because it better informs prospective patients of remedies and builds bridges between doctors and patients. However critics argue that the pharmaceutical industry is inventing diseases and hyping public concerns to increase sales of brand name medications, from propecia for baldness (despite its side effects of potentially permanent loss of libido) to botox for wrinkles. Ray Moynihan describes this in the BMJ as the corporate sponsored creation of disease – in which a cohort of researchers with close ties to drug companies, work with colleagues in the pharmaceutical industry to develop and define new categories of illness. However Metzel points out the most outstanding features of this process not highlighted by Moynihan is that pharmaceutical ads overwhelmingly focus on women. Sarafem another brand name for fluoxetine (Prozac) has for instance been marketed to “treat” “Premenstrual Dysphoric Disorder” – psychologizing and the treating with drugs seemingly normal women’s life events such as menstruation, menopause, sexuality and motherhood. Both these and the earlier ads targeting doctors cast womens’ mental health in the light of expectations for their role in society, positing psychotropic medications as agents for restoring “normal” womanhood. Metzel documents how changing trends in the depiction of women from domineering “momism” through the perceived hostility of womens lib became reflected in ads for antipsychotics like mellaril depicting domineering women whose hostility threatened to upend their husband’s mastery of the family situation and those for valium depicting the socially frustrated women we have seen in the above passages whose relationships have failed with men. A valium ad used the words of equal rights to genderize anxiety - “separate but not equal” to describe women’s anxieties and tensions. Some studies found that valium was 70% overprescribed to women by comparison with men. Instead of being images dreamt up by marketing executives, Metzel says drugs adverts show how an entire system regarded its female patients, because they “illustrate the ways in which these new scientific treatments could not function free of the culture in which they were given meaning”. They are, he argues, representative of the same “gendered assumptions” at play in medicine and society.

Fig 13: Seroquel (quetiapine fig 2) advertisement

With the changing political climate of feminism becoming mainstream and more women entering the medical profession, the thrust of advertising has moved out of medical journals into the mainstream of Newsweek and Time, appealing strategically to the female patient as well as her doctor. Metzel comments that this extends the role of medication helping women suffering anxiety and depression into a territory where it is claiming that women’s ambitions and social concerns can be treated or normalized with psychotropic medications becoming a form of social engineering for profit by pharmaceutical companies.

In a 2010 Money Watch article “AstraZeneca’s New Seroquel Ad Has 5 Pages of Legal Disclaimers”, Jim Edwards of CNN notes that the ad campaign run in major news magazines had no less than five pages of legal disclaimers concerning possible side effects including high blood sugar and diabetes, weight gain, "potentially fatal" neuroleptic malignant syndrome (fever, rigid muscles, confusion), "tardive dyskinesia (TD) - uncontrollable movement of the face, tongue,
other parts of the body”, Cataracts, Suicidal thoughts, “Priapism” (an erection that won't go away), in the wake of their successful winning of six legal victories over collective action suits by 10,000 plaintiffs who claim Seroquel, the $1.2 billion-per-quarter selling drug, causes weight gain and diabetes.

In 2009 AstraZeneca (AZN) agreed to pay $520 million in a settlement with the U.S. District Attorney in Pennsylvania to end a probe of its marketing practices on the atypical antipsychotic, which allegedly resulted in off-label use of the drug in children and the elderly. According to AZ’s own disclosures, the cost of its alleged malfeasance on Seroquel will top $1.1 billion. According to Attorney General Eric Holder AstraZeneca was charged with fraudulently marketing Seroquel and promoting the drug to patients and physicians for uses that the Food and Drug Administration never approved. "These were not victimless crimes," said Holder. "Illegal acts by pharmaceutical companies and false claims against Medicare and Medicaid can put the public health at risk, corrupt medical decisions by health care providers, and take billions of dollars directly out of taxpayers' pockets." On top of the $520 million fine, AstraZeneca said it would enter into a five-year compliance agreement with the Department of Justice.

The Justice Department alleged that, between 2001 and 2006, AstraZeneca promoted Seroquel for certain uses not approved by the FDA as safe and effective, including for dementia in the elderly. The government alleged the company paid doctors to speak at events to other doctors about unapproved uses of Seroquel, among other allegations. The pharmaceutical giant has also been accused of violating anti-kickback laws, by paying doctors to refer the drug to patients, while at the same time bringing in money from government health care programs. The DOJ says AstraZeneca targeted "doctors who do not typically treat schizophrenia or bipolar disorder, such as physicians who treat the elderly, primary care physicians, pediatric and adolescent physicians" and used ploys to get doctors to write off-label prescriptions for its psychotropic drug, including paying them fees for articles and studies ghostwritten by company reps on research the doctors hadn’t seen.

<table>
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<th>Comparator</th>
<th>Anxiety</th>
<th>Total BPRS</th>
<th>Factor I</th>
<th>Factor V</th>
<th>Hostility</th>
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<th>Mood Cluster</th>
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<td>-</td>
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</tbody>
</table>

(Exhibit 2 § 3.) According to the accompanying legend, a ✓ was entered on the chart where Seroquel showed a “statistically significant benefit.” (lid) That mark only appeared in relation to tests against placebo. (lid) For all other comparators, the comparator drug either “demonstrated significant superiority compared to Seroquel” (marked by an ✸), or showed no statistically significant difference (marked -). (lid) Technical Document 4 concluded:

Conflicts of interest abound in the marketing of seroquel. In 2009, the Chicago Tribune and ProPublica reported that Chicago psychiatrist Michael Reinstein, who wrote 41,000 prescriptions for Seroquel, received $500,000 from AstraZeneca. Until a Philadelphia Inquirer expose in the same year, Florida child psychiatrist Jorge Armenteros, a paid AstraZeneca speaker, was chairman of the FDA Psychopharmacologic Drugs Advisory Committee responsible for recommending Seroquel approvals.

A further demonstration of the widespread miss-prescription of antipsychotics comes from a 2015 BMJ article (doi: 10.1136/bmj.h4326) widely reported in Science and New Scientist, that shows the drugs are routinely used to pacify people with mental disabilities who have no symptoms of psychosis, rendering them even more disadvantaged than they need to be.
In 2015 GlaxoSmithKline finally gave independent researchers access to the full data set of study 329, originally published in 2001. The first paper from the trial, published in 2001, involved 275 teens with depression. It concluded that paroxetine (prozac) was generally well tolerated and had similar side-effect rates to placebo pills. But by then several US lawsuits were under way, involving adults who had become suicidal or violent soon after starting these types of drugs. Paroxetine manufacturer GlaxoSmithKline later released trial reports revealing that teens in the study had higher rates of self-harm and threatening to commit suicide than those on placebos. Sifting through the released data, David Healy and his team found 15 instances of suicidal behaviour among 12 teenagers taking the drug, compared with four in the similarly sized placebo group (BMJ, DOI: 10.1136/bmj.h4320). The company’s trial reports had suggested only 10 instances in those taking paroxetine.

In some of the UK’s poorer areas, one in six people is on an SSRI, and traces of Prozac have turned up in the water supply. Another 2015 study found that under-25s taking them are more likely to commit violent crime (PLoS Medicine, DOI: 10.1371/journal.pmed.1001875). A major review in 2008 showed that SSRIs work no better than placebo for mild depression. Tim Kendall of the Royal College of Psychiatrists in London says a large body of evidence now shows talking therapies like cognitive behavioural therapy should be the first port of call in depression, especially for those under 30. To GSK’s credit, the firm is the only drug company so far signed up to AllTrials, a campaign for disclosure of clinical research data.

The American Medical Association has called for a ban on advertising prescription drugs and medical devices directly to consumers, saying the ads drive patients to demand expensive treatments over less costly ones that are also effective. The influential doctors’ group said the new policy reflects physicians’ concerns that marketing spending on a proliferation of advertising is helping to drive up drug prices. The group voted at its annual meeting in Atlanta to support a ban. The United States and New Zealand are the only two countries that allow direct-to-consumer advertising of prescription drugs. A series of court decisions has determined the ads cannot be banned outright because they are a form of commercial speech protected by the U.S. Constitution. According to a U.S. Food and Drug Administration analysis this year, 52 percent of Americans believe direct-to-consumer ads do not have enough information about risks and 46 percent say the ads lack information about benefits (Kelley S 2015 U.S. doctor group calls for ban on drug advertising to consumers Reuters17 Nov).