

## Data Based Medicine Position Paper: Mood Stabilizers for Prescribers

**DRAFT**

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### Contents

THE “MOOD STABILIZERS” .....	3
DRUGS AND CHEMICALS .....	3
<i>WHAT STUDIES HAVE BEEN DONE ON THESE DRUGS?</i> .....	4
<i>WHAT DATA UNDERPIN THE USE OF THESE DRUGS?</i> .....	4
<i>HAS ANYONE ACCESS TO ALL THE DATA?</i> .....	4
<i>WHAT PUBLICATIONS ARE THERE ON THE USE OF THESE DRUGS?</i> .....	4
<i>HOW GOOD ARE THESE STUDIES?</i> .....	5
<i>ARE THERE ANY PROBLEMS IF I KEEP TO RECOGNIZED GUIDELINES?</i> .....	5
<i>WHERE CAN I GET USEFUL INFORMATION ON THE MOOD STABILIZERS?</i> .....	6
THE BENEFITS OF MOOD STABILIZERS .....	6
<i>DO MOOD STABILIZERS WORK?</i> .....	6
<i>WHAT DO MOOD STABILIZERS DO?</i> .....	6
<i>WHAT OVERALL IMPACT WILL MOOD STABILIZERS HAVE ON THE PATIENT FUNCTIONS?</i> .....	7
ACUTE TRIALS & CHRONIC TREATMENT .....	8
<i>IF THE PATIENT IS SEVERELY ILL WHAT TREATMENT SHOULD I PRESCRIBE?</i> .....	8
<i>ARE THE EFFECTS OF MOOD STABILIZERS ALL IN THE MIND?</i> .....	9
<i>SHOULD I PRESCRIBE 4-5 MOOD STABILIZERS TOGETHER?</i> .....	9
<i>WHAT CAN I DO TO GET THE PATIENT BETTER?</i> .....	9
<i>MYTHS ABOUT MOOD STABILIZERS</i> .....	9
QUESTIONS SPECIFIC TO THIS PATIENT .....	11
<i>WHAT DO I KNOW OF THIS PATIENT’S PROS &amp; CONS?</i> .....	11
<i>WHAT ARE THIS PATIENT’S OPTIONS?</i> .....	11
<i>DO THE PEOPLE IN THE STUDIES OF THESE DRUGS RESEMBLE THIS PATIENT?</i> .....	11
<i>IS THERE ANY WAY TO KNOW WHICH MOOD-STABILIZER TO GIVE THIS PATIENT?</i> .....	11
<i>HOW DO I KNOW WHICH DRUG TO PRESCRIBE?</i> .....	11
<i>HOW LONG DOES THE PATIENT HAVE TO BE ON TREATMENT?</i> .....	12
<i>WHAT ARE THE RISKS?</i> .....	12
<i>HOW LIKELY ARE THE LISTED SIDE EFFECTS OF MOOD STABILIZERS TO HAPPEN?</i> .....	13
<i>WHAT UNACKNOWLEDGED RISKS CAN REASONABLY BE SUSPECTED?</i> .....	13
<i>HAVE I ACCESSED ANY INDEPENDENT DATA ON THE RISKS LINKED TO TREATMENT?</i> .....	13
<i>PERIODS OF RISK</i> .....	13
<i>THE CAUSE WORD</i> .....	13

*STOPPING?*..... 14  
*WHAT IS THIS PATIENT'S RISK OF STOCKHOLM SYNDROME?* ..... 14  
*WHAT KIND OF DOCTOR AM I?* ..... 14  
*COULD MY JUDGEMENT BE AFFECTED IN ANY WAY BY A TARGET I SHOULD MEET?* ..... 15  
APPENDIX – MOOD STABILIZERS..... 16

DRAFT

## THE “MOOD STABILIZERS”

“Mood stabilization” is a close to perfect marketing term popularized by Abbott when marketing Depakote. It essentially didn’t exist before 1994. Since then sections on mood stabilizers have appeared in all books on psychotropic drugs, where they never existed before and nobody seems concerned - in much the same way as in Season 4 of Buffy the Vampire Slayer, Buffy was given a sister, who hadn’t featured before and no-one seemed bothered<sup>1</sup>.

The words mood and stabilization give the impression that these drugs have a prophylactic effect – that is that they will ward off future episodes of depressive or manic mood. There is no good evidence that the drugs will do this – the reason they are called mood stabilizers is because it would in fact be illegal to state they are prophylactic. The drugs in the group are otherwise used as anticonvulsants and antipsychotics (see Guidance on Antipsychotics).

The mood stabilizers are a valuable group of drugs. The authors of this guideline prescribe some of them regularly. But we believe their safe use is threatened by misinformation and complacency. This guidance highlights the poor quality of the evidence underpinning their use.

Other guidelines are based on the published scientific evidence. As things stand this is a recipe for handing medical care over to pharmaceutical companies. This guidance in contrast involves judgment calls but we outline the principles that underpin our judgments so that readers can see where further evidence may in due course reduce the need for clinical discretion and where the need for discretion is likely to remain. Safe and effective treatment needs an observant patient and a wise doctor - a team like this should turn to the “evidence” with caution<sup>2</sup>.

## GENERAL ISSUES

### DRUGS AND CHEMICALS

Drugs are chemicals that may be useful in the management of a medical condition. It used to be doctors and patients who decided what were “diseases” and what needed treating – it is increasingly drug companies who shape this. Clinical trials were discovered by medicine in the 1950s as a means to weed out ineffective treatments. Patients then took the risks of trying out possibly dangerous new drugs in these trials on behalf of their families, and the communities from which they came and in so doing they freed us from many scourges that for millennia had been killing children prematurely or leaving people crippled. In other words, companies make chemicals in laboratories, but we make drugs in clinics.

This worked so well at first that clinical trials were adopted as a gateway to the marketplace for candidate drugs. What should happen is that informed of the risks, patients who volunteer get given the candidate, an old drug or a placebo. The outcome of the study – positive or negative – is then written up in an academic article, with the raw data publicly available to other investigators to scrutinize.

Companies submit the trials to national regulators (such as FDA) seeking a license to market drug X as a

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<sup>1</sup> D Healy (2008). Mania. Johns Hopkins University Press.

<sup>2</sup> See False friends and related posts on davidhealy.org

treatment for condition Y. The regulator's brief is to monitor marketing claims – it is not to make sure the drug is good for you or is as good as other drugs on the market.

But this is not what happens. And no one seems to have the brief to work out if the drug is good for you or as good as other treatments on the market.

### **WHAT STUDIES HAVE BEEN DONE ON THESE DRUGS?**

Almost all studies on the antidepressants have been carried out or commissioned by the pharmaceutical companies that produce them. There are a vanishingly small number of independent studies. No government agency or independent authority runs studies. There are a number of independent studies of lithium, which suggest it is much better than anything else available but no company stands to make money out of lithium.

### **WHAT DATA UNDERPIN THE USE OF THESE DRUGS?**

The data from clinical trials of mood stabilizers is almost universally unavailable. For this reason practicing properly Data Based Medicine (DBM) is impossible and needs to be supplemented with clinical judgment.

### **HAS ANYONE ACCESS TO ALL THE DATA?**

No-one has seen or has had access to all the data, not even regulators such as FDA.

### **WHAT PUBLICATIONS ARE THERE ON THE USE OF THESE DRUGS?**

There have been over a thousand published clinical trials involving mood stabilizers.

Of the published studies most - 50-90% - appear likely to have been ghostwritten – written by a professional writer on behalf of a pharmaceutical company and published under the name of eminent physicians who may not have read the actual text. Or else the studies will for the most part have been written within the pharmaceutical company.

For the most commonly prescribed mood-stabilizers up to 50% of the studies are likely to be unpublished<sup>3</sup>.

Based on what is known about the antidepressants, in perhaps around 30% of published mood stabilizer studies that claim these drugs work well, it seems likely that if they had the data independent experts would conclude that the study showed the drug did not work.

For instance in a study looking at the long-term benefits of Abilify (aripiprazole) the drug failed to distinguish from placebo in over 30 centers in the US, but showed a big difference from placebo in two centers in Mexico. Adding in the data from the Mexican centers made Abilify look slightly better in terms of relapse overall. In none of the articles about this study or the benefits of Abilify is this aspect of the data revealed. FDA were aware of the issue but chose not to investigate<sup>4</sup>.

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<sup>3</sup> Turner EH, Matthews AM et al (2008). Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 358, 252-260.

<sup>4</sup> Rosenlicht N, Tsai AC, Parry PI, Spielmans G, Jureidini J, Healy D (2012). Aripiprazole in the maintenance treatment of bipolar disorder: A critical review of the evidence and its dissemination into the scientific literature. PLoS Medicine, 8, e10000434.

For many published studies of there are multiple publications – the record appears to be 234 publications from 4 Zyprexa (olanzapine) studies, none of which contain a clear picture of the weight gain, raised lipid levels, or glucose levels or rates of suicide this drug can cause.

Many articles outlining the risks of mood stabilizers have not been published owing to concerns in the legal departments of medical journals that they will be sued by pharmaceutical companies and a general bias against publishing even convincing case studies that outline the hazards of treatment.

### HOW GOOD ARE THESE STUDIES?

Even if all studies were published by real authors, there would be a problem. Almost all the studies that have been done have lasted only a few weeks. They do not look at outcomes that matter to patients such as whether I live or die, get back to work, or have a better quality of life. The rating scales used to decide if the drugs work in fact can show an improvement in your clinical state even if all that is happening is that you are suffering from side effects.

Some of the claims that antipsychotics work as mood stabilizers are based on recent studies that have stabilized patients on treatment and then randomized some to continue with treatment and others to placebo. Those remaining on the drugs do better. But all the drugs in this group are linked to dependence and withdrawal syndromes, and common sense suggests that what's going on here is that those remaining on drug are not doing better – they just aren't going into withdrawal.

The short duration of these studies mean that anyone on these drugs for more than a few weeks is flying blind. We don't know what could happen. It is as if around week 8 or so you were switched from a drug to a chemical. Drugs are chemicals that come with information. Chemicals are chemicals.

### ARE THERE ANY PROBLEMS IF I KEEP TO RECOGNIZED GUIDELINES?

Our criterion for a good Quality guideline is that it is based on data rather than published evidence. Based on this criterion, there are no guidelines for the use of mood-stabilizers that warrant a Quality Mark greater than 1 out of 10.

It is customary to think that independent guidelines are superior to guidelines linked to pharmaceutical companies. But in fact both sets of guidelines are identical and independent guidelines may be more dangerous by virtue of their apparent independence.

When the Cochrane Center reviewed the antidepressants, they concluded that Sertraline (Zoloft) was among the most effective and safest, but taking unpublished data into account it ranks among the least effective.

When the Cochrane Center first reviewed the use of antidepressants for children, they concluded these drugs were safe and effective but when unpublished data became available it was clear they weren't.

When the Cochrane Center first reviewed the evidence on Tamiflu they concluded it was beneficial but when unpublished data became available they had to revise their view.

## WHERE CAN I GET USEFUL INFORMATION ON THE MOOD STABILIZERS?

At the moment we are in the midst of a full-blown mania for bipolar disorders and it is very difficult to get sensible advice anywhere. We are in a world where if it is detected that someone has felt good even for a few hours at some point, they are likely to be diagnosed as bipolar and treated accordingly.

## THE BENEFITS OF MOOD STABILIZERS

### DO MOOD STABILIZERS WORK?

If the question is do these drugs tranquilize or sedate and can this with appropriate teamwork between doctor and patient be put to useful purposes, then the answer is Yes. But if the question is what have controlled trials shown, then the answer may be No.

Other than for monitoring safety, controlled trials aren't needed when a treatment unequivocally does something either good – for instance coal tar for strychnine poisoning or penicillin for septicemia - or hazardous - for instance SSRIs and altered sexual functioning. Controlled trials are primarily done in the case of the mood-stabilizers because there is a real doubt as to whether they work or not and in this case there are no trials that show clearly that any of the drugs from this group ward off episodes of mood disorder.

Most of the drugs in the group can be effectively anti-manic. Except for lithium the anti-manic effects are probably primarily the result of sedation. Lithium is also anti-manic but seems to exert this effect without being sedative. In addition except for lithium, these drugs are not actually prophylactic for mood disorders.

For most people saying a treatment “works” suggests it saves lives, or enables people to return to work, or makes the chances of an illness returning in the future less likely.

As of 2009, the trials that had been done for anticonvulsants and antipsychotics showed more deaths in those on these drugs than on placebo. In this sense, the drugs don't work.

There is no evidence that the mood-stabilizers get people back to work – no one has ever attempted to investigate this.

There is considerable evidence that mood-stabilizers may make future episodes of depression or mania or other nervous problems more likely.

### WHAT DO MOOD STABILIZERS DO?

The mood stabilizers are group of very different drugs that act in quite different ways; they include a number of anticonvulsants, antipsychotics and lithium.

There are three different groups of anticonvulsants. One inhibits sodium reuptake, one acts on the GABA system, one inhibits carbonic anhydrase; some of the group have two of these actions and some all three. These actions have quite different effects that remain almost entirely unexplored so that your doctor is unlikely to be able to tell you what exactly she wants the drug to do for you or what behavioral effect the drug is likely to have on you. There are other anticonvulsants like Keppra (leviracetam) whose mode of action remains unknown.

Many recent antipsychotics have been touted as mood-stabilizers. All of these block dopamine receptors – and this tranquilizes which is not the same thing as stabilizes.

Lithium in contrast does an extraordinary number of things in the body but no-one is clear on what are its key actions. In addition being helpful in mood disorders, it appears to have anti-aggressive or anti-impulsive effects.

These are very different drugs, but you'd never guess it from their marketing which makes them all look the same. This is because the evidence is mostly produced by pharmaceutical companies and is designed for market purposes, rather than to offer insights on what the drugs actually do and who would be best treated with which drug.

To make this point more clearly, in the past many other drugs such as antidepressants, minor tranquilizers and others have been billed as stabilizing moods. In many cases there is better evidence for the antidepressants as “mood-stabilizers” but the antidepressants are now “branded” as mood disrupters.

None of these drugs in other words corrects an abnormality. All of them can do something useful. A number of the anticonvulsants, such as sodium valproate can reduce impulsivity and irritability for some people but not all. Lithium does something similar – for some but not others. The antipsychotics were formerly called major tranquilizers and this is essentially their primary action – they reduce tension and irritability.

#### **WHAT OVERALL IMPACT WILL MOOD STABILIZERS HAVE ON THE PATIENT FUNCTIONS?**

A mood stabilizer may dramatically shorten a manic episode, save a life and get the person back to work but when used chronically there can be risks. One of the better and more independent studies from 1980 showed that patients on antipsychotics for instance were less likely to be readmitted to hospital if taking their medication continuously but also less likely to get a job or get married<sup>5</sup>.

For someone who has been ill for a relatively brief period of time and improves, their recovery is likely to be due to some combination of time, placebo or acute drug effects and the clinical issue is then ensuring the person can get off treatment. If the patient can identify a very clear benefit from the drug they are on – such as an anxiolytic effect – there is a better chance that a specific drug effect rather than generic placebo factors are making a difference. This is especially true for lithium.

For patients whose moods chronically swing, it becomes more likely the treatments are making things worse. One hundred years ago before these treatments came into being, people with severe manic-depressive illness had on average fewer episodes than people with milder mood disorders have today. Unless the patient can identify a clear benefit there may be a case for not having them on drugs that do not work for them.

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<sup>5</sup> Johnstone EC, Crow TJ, Frith CD, et al. The Northwick Park ‘functional’ psychosis study: diagnosis and treatment. *Lancet* 1988; ii:119–125.

In terms of function, we doctors should ask ourselves this question – if I were on this cocktail of drugs in this dose, how would I function – and if the answer is I probably wouldn't be able to do much, the dose or number of drugs should be reduced.

### **ACUTE TRIALS & CHRONIC TREATMENT**

In the 1960s the first trials of the antipsychotics assumed they were like antibiotics and as a result the trials only lasted a few weeks. Trials today still only last a few weeks, even though many people are likely to be on treatment for years. Trials this short produce a sign the drugs may work rather than evidence they are helpful long term. If the drug gets through trials like this and gets on the market, this is the point at which the research to work out who benefits from this drug should start – but this research doesn't happen.

The trials for the anticonvulsants and lithium have lasted longer. The anticonvulsants have not been shown to be prophylactic. Lithium may be, but the patients must remain on it for over two years to reduce the likelihood of a further episode. Some people remaining on lithium may become dependent and trying to withdraw can trigger problems.

Having any drug chronically is a recipe for extensive changes elsewhere in the body that will almost certainly not have been investigated. In the case of the antipsychotics this leads to diabetes, raised cholesterol levels, and an increased rate of heart attacks and strokes – the list of complications is growing. As the examples of nicotine, HRT, alcohol or other drugs taken over time show, it is all but certain that other problems will emerge in some who take mood-stabilizers for years.

### **IF THE PATIENT IS SEVERELY ILL WHAT TREATMENT SHOULD I PRESCRIBE?**

For severe unstable mood disorders, there are difficulties in working out what is caused by the illness and what by treatment. Unstable mood disorder was extremely rare before current treatments were introduced. Many of us have favorite combinations of drugs – anticonvulsant, with antipsychotic and lithium – for tackling treatment resistant cases. None of these combinations have ever been shown in controlled trials to work reliably.

If the patient does not show a rapid response to the addition of another drug, you should probably not keep them on any combined treatment for long. It is more likely that something in the combination of treatments is holding them back than it is that the combination will suddenly start helping.

For more severe manic-depressive illness, there is no good treatment. The optimal treatment will reduce the number of hospitalizations a patient has over time. Reacting too quickly to a hospitalization by changing drug or adding to a cocktail is often the wrong move – it might be best to aim at hospitalization less often rather than never and being out of action for shorter periods of time rather than never out of action.

At present it is fashionable to say antidepressants should not be given for manic-depressive illness. There is no good evidence for this – except for the evidence that antidepressants can for some people increase the frequency of depressive episodes over time but so can mood-



stabilizers. If severely depressed there is no obvious reason for not having an effective (older) antidepressant.

#### **ARE THE EFFECTS OF MOOD STABILIZERS ALL IN THE MIND?**

No. But people on placebo have as few illness episodes as those on mood stabilizers in clinical trials. What these data show is that a surprising number of people with manic-depressive illness do as well on less or no medication or therapy as they do on the latest blockbuster.

If the question in these trials had been do anticonvulsants have an anti-impulsive effect or do antipsychotics tranquilize, the answer would have been Yes. No one wants to run this kind of trial as it would leave it to the clinical discretion of the doctor to use the drugs wisely – and clinical discretion is not in fashion. What the current trials show is that many doctors when they see a patient improve on treatment assume that it is the treatment that has produced the benefit – without asking the patient whether they can detect anything useful the treatment is doing. If there are side effects they attribute them to the illness rather than the pill.

#### **SHOULD I PRESCRIBE 4-5 MOOD STABILIZERS TOGETHER?**

No.

The reason these combinations get prescribed is that each drug in the group has been through clinical trials and these trials have supposedly shown the drug works. For someone who is not getting better, it may seem to make sense to have them on 4-5 drugs all of which have been shown to work. But the trials have not shown these drugs work in the sense that parachutes work or putting a dislocated shoulder back into place works. Trials are not needed when treatments work in this sense.

What the trials have shown is that it is not right to say the drugs do nothing. It might make sense to be on 4-5 drugs that work but it makes less sense to put someone on 4-5 drugs about which all we know is that it is just not right to say that they do nothing? The one thing we do know is that no-one has investigated the effect of combining them.

#### **WHAT CAN I DO TO GET THE PATIENT BETTER?**

Manic-depressive illness has recently been rebranded as bipolar disorder. For some people, the best way to help them might be to change their diagnosis. Many people who would until recently have been diagnosed as anxious or depressed have under relentless company marketing been re-diagnosed as bipolar and as a result are now exposed to far more toxic drugs than is good for them. This is especially true for children.

Severe manic-depressive illness – that leads to hospitalization – is a relatively rare disorder than can be very difficult to treat. It is probably important to marry patience (episodes will clear up with time 16 – 24 weeks whether treated or not), with good hygiene - attention to physical activity, diet, sleep hygiene and limiting alcohol or other substances, along with problem solving issues in relationships or at work.

#### **MYTHS ABOUT MOOD STABILIZERS**

1. Mood Stabilizers, especially antipsychotics, are neuroprotective.

This quite extraordinary claim is used to justify early intervention, even in children. The antipsychotics in particular are associated with much more obvious and visible brain damage than can be found with ECT. This is not a recipe for not using them but does suggest using just the same caution as you would take to having ECT. Children seem most at risk from the harmful neurological effects of mood-stabilizers.

2. Suicide on antidepressants stems from unrecognized bipolar disorder

Faced with a controversy about the antidepressants triggering suicide, pharmaceutical companies helped promote the idea that what was happening was that those committing suicide were untreated bipolar disorder patients who would have been fine if they'd been put on a mood-stabilizer. This controversy was actively used to create a bipolar market.

The facts are that even healthy volunteers can become suicidal on antidepressants and commit suicide. And in placebo controlled trials the mood-stabilizers cause suicide in bipolar disorders and schizophrenia, as well as in epilepsy, migraine and other conditions.

3. There is a chemical imbalance in manic-depressive illness.

No one knows what causes severe manic-depressive illness. A serious imbalance in the marketing of drugs has led to most diagnoses of bipolar disorder.

4. Manic-depressive illness starts in childhood.

Until a few years ago the idea that bipolar disorder might have its onset before puberty would have been laughed out of court. But now even what was once called the terrible twos – a normal stage of childhood development – is liable to attract a diagnosis of bipolar disorder. As a result children are being put on some of the most toxic drugs in medicine – almost as though common colds were to be treated with the kinds of drugs used for cancer.

5. Mood-stabilizers do not cause Addiction

Many anticonvulsants and antipsychotics cause people to be hooked to them – it becomes impossible to stop because of how bad the person feels on stopping and the relief from restarting treatment. Some drugs are worse than others. Because companies have denied there is any problem, it is difficult to know which drugs are the worst offenders and how to manage the problem (See DBM Stress Syndromes and DBM Withdrawal).

Companies and their experts refer to discontinuation syndromes – another term for withdrawal or being hooked. It is not uncommon to hear people say it is harder to get off antipsychotics than off opiates, or benzodiazepines.

It is in areas like these – mythologies about chemical imbalances and addiction - that doctors need to help patients and patients need to help doctors to escape the clutches of company marketing that has been so successful that many will be astonished to know that things they have taken from granted have no basis in science.

## QUESTIONS SPECIFIC TO THIS PATIENT

### WHAT DO I KNOW OF THIS PATIENT'S PROS & CONS?

The risks they might be happy to live and the one's they wouldn't, and how important improvement is compared to other things in their life?

### WHAT ARE THIS PATIENT'S OPTIONS?

Unless there is a real risk of danger to self or others, and good evidence of a beneficial response to treatment, there are always other options. It's a matter of finding them – but this is made difficult at the moment by the fact that increasingly doctors face the sack if they deviate from a conventional line.

We are in a world, where the slightest bit of good mood at some point in time, or disinhibition caused by a prior drug you were on, could lead to a diagnosis of bipolar disorder and a lifetime of treatment with drugs that carry significant risks.

### DO THE PEOPLE IN THE STUDIES OF THESE DRUGS RESEMBLE THIS PATIENT?

Many of the people in mood-stabilizer trials were recruited by advert, a lot were volunteered by their doctor rather than volunteered themselves, none gave informed consent, some didn't exist. There were very few average people in these trials. There were vanishingly few patients with conditions in addition to bipolar disorder.

### IS THERE ANY WAY TO KNOW WHICH MOOD-STABILIZER TO GIVE THIS PATIENT?

There is no research on this important question. It can only be established by trial and error and you should be prepared to switch drugs around to find one that best suits this person.

### HOW DO I KNOW WHICH DRUG TO PRESCRIBE?

Before starting a drug, unless the person has been on it before, no can know how they will respond to it. Lots of work could have been done to match people to treatments but this hasn't been done – probably because research like this would have greatly reduced market share for blockbusters.

If put on an anticonvulsant, lithium or an antipsychotic, the taker should clearly be able to identify a benefit in the first few hours or days. The drug should make them feel less bothered and if this feels good to them, the treatment may be useful over the longer run. Sometimes despite feeling a benefit moods may continue to swing but this will not be because the drug is not working. Something else is also needed.

There is a good chance that anyone trying an anticonvulsant will find it makes them more labile, irritable or impulsive rather than less. The important thing here is to switch to another drug which may have quite a different effect. Similarly, on trying an antipsychotic the taker may find it profoundly dysphoric but switching to another one may produce a useful tranquilization. If there is no clear benefit, and in particular if the person feels worse in any way, they are likely on the wrong drug, or on too high a dose of the drug. The problem will rarely be because too low a dose and changing drug rather than increasing the dose is likely to be safer.

### HOW LONG DOES THE PATIENT HAVE TO BE ON TREATMENT?

A diagnosis of bipolar disorder sentences most people to a lifetime of treatment often with cocktails of drugs. Even some of the most severely ill people have learned not to take their treatments in between clinic visits and in many cases this subterfuge appears to do no harm. You may want to revisit the diagnosis, especially if the diagnosis was made after only one significant episode of either depression or elevated mood.

### WHAT ARE THE RISKS?

The lists below are not exhaustive. On RxISK.org we hope to investigate the views of those taking these treatments as to how these risks stack up in order of significance.

The standard list of side effects in the manufacturers information leaflets for antipsychotics include motor problems such as Parkinson's syndrome, a range of abnormal motor movements (dyskinesias), and painful muscle cramping (dystonias), some of which can be permanent, a state of intense inner restlessness (akathisia), marked weight gain, sexual dysfunction, sedation, constipation, fainting, palpitations, sweating, tremulousness, headache, blurred vision, rashes, and many more.

For anticonvulsants they include sedation, weight gain, irritability and restlessness, disinhibition, dizziness, disorientation, concentration and memory problems, nausea, cardiac problems, fatigue, skin and visual disturbances.

For lithium they include fatal toxicity in overdose, tension and restlessness, weight gain, kidney problems, thyroid problems, disorientation, fatigue, concentration and memory problems.

Depending on the Drug, mood-stabilizers can also cause:

- Dependence leading to significant withdrawal problems (up to 50%),
- Anxiety or agitation – severe in 20% of cases
- Diabetes in the case of the antipsychotics especially olanzapine.
- Suicide – up to 1 in 100 will engage in a suicidal act, and a large number will succeed – this is probably not the case with lithium.
- Violence, aggression and irritability – this affects an unknown number of people, and again seems less likely with lithium.
- Neuroleptic malignant syndrome – a potentially lethal complication of antipsychotics.
- Tardive dyskinesia – probably as common in new as in old antipsychotics and likely to happen in children if they are put on antipsychotics, and perhaps more common in mood disorders than in schizophrenia.
- Demotivation – antipsychotics are profoundly demotivating. They take the color out of life and leave someone less likely to do anything. Doctors and other healthcare workers should ideally try these drugs themselves and find out how difficult it is to do much while on them.
- Disinhibition – the anticonvulsants can make patients suicidal – even patients with no mental health problems being treated for epilepsy or migraine can be made suicidal. We need good descriptions of what changes in people on these drugs to produce this outcome.

### **HOW LIKELY ARE THE LISTED SIDE EFFECTS OF MOOD STABILIZERS TO HAPPEN?**

No one knows. Company answers are that if they have happened even once we have to list them. This implies they are rare. But in fact side effect data are not collected properly. There is almost no-one put on an antipsychotic or anticonvulsant who will not have significant side effects. Anyone put on them needs a chance to balance the benefits they get against the problems the treatment may cause.

### **WHAT UNACKNOWLEDGED RISKS CAN REASONABLY BE SUSPECTED?**

On launch the mood-stabilizers should have come with clear statements about the risks of dependence, withdrawal, suicide, diabetes, metabolic syndrome and other difficulties. We simply do not know what other effects chronic actions on the brain systems these drugs work on might trigger for good or bad.

### **HAVE I ACCESSED ANY INDEPENDENT DATA ON THE RISKS LINKED TO TREATMENT?**

#### **PERIODS OF RISK**

Just as for space shuttles, many of the dramatic problems mood-stabilizers cause cluster around take-off and landing (starting and stopping). The first few days of exposure to either an antipsychotic or anticonvulsant can be associated with agitation up to and including suicide. Problems also emerge when the dose is being reduced or shortly after the treatment is stopped. Difficulties also arise in the course of treatment when the dose is changed.

Aside from risk periods like these that are associated with agitation and dependence, there are a range of problems that may appear in the course of treatment and in some instances endure long after treatment stops.

#### **THE CAUSE WORD**

Companies typically deny their drug causes any problems and are close to allergic to the word cause. You should use it where possible. One company tactic is to claim that there is no evidence their drug causes a problem unless a clinical trial has shown that their drug is statistically significantly more often linked to the problem than placebo. Without data like this companies are happy to deny a link for ever – even in the face of convincing evidence of a problem emerging on treatment, clearing when the treatment is stopped and reappearing when treatment is restarted.

When an event like diabetes happens, company strategies have been to say that their drugs do not cause it, that it is caused by weight gain which their drugs also do not cause. They may concede their drug increases appetite but lay the blame for giving in to your appetites on the patient or their doctor's failure to warn of the need for a healthy lifestyle.

Companies will go to extraordinary lengths to avoid linking their brand to a problem – a key defense is to direct the questioner to a medical academic. Academics unlike companies can say whatever they want – and can be depended on to say the drugs do not cause any problems.

Finally faced with enquiries on risks from dependence to birth defects or diabetes, companies will typically suggest you Talk to your Doctor. But your doctor will only have the public domain information that denies a link to problems and will be completely unaware that internal company

determinations in many cases will have decided their drug causes the problem you have. This is a way to pin legal liability for problems on the doctor.

### **STOPPING?**

Taking and stopping a mood-stabilizer is not the same as never-taking. These drugs come with significant withdrawal and legacy effects.

Depending on the drug up to 50% of people may have difficulties with withdrawal (See DBM withdrawal guidance). It may be possible to minimize withdrawal problems by tapering the drug very slowly using liquid formulations. But this doesn't work for all and for many withdrawal especially from antipsychotics may be impossible.

The issue may be complicated by legacy effects of antipsychotics. Some people seem to develop a dysthymia that becomes manifest as they try to stop treatment. This does not seem to be withdrawal. Some features such as dysthymia, an intolerance for stress or memory difficulties can endure for years after treatment stops.

Antipsychotics and anticonvulsants can blunt normal emotions such as anger. Stopping them can lead to a resurgence of these emotions causing problems in anyone who is no longer used to dealing with them.

### **WHAT IS THIS PATIENT'S RISK OF STOCKHOLM SYNDROME?**

Stockholm syndrome happens when a person's life is in danger, when they are isolated and when their captor is kind. They end up identifying with their captor and wanting to keep him/her happy.

Illness puts someone in danger and isolates them and doctors today are increasingly trained to be nice to patients. But your training has not taken into account that when asked about problems even the most sophisticated patients who are having grave difficulties from treatment will likely tell you that everything is going wonderfully or at best hint obliquely about problems.

Unless you have reported adverse events on drugs, even though otherwise wonderful you are probably likely to be just the kind of doctors at most risk of inducing Stockholm syndrome.

### **WHAT KIND OF DOCTOR AM I?**

Just as they would do for any consumer, companies segment doctors into types.

High Flyers are those doctors who prescribe the latest drug, for the newest indication, often in the highest doses, or in combinations, often before many of their colleagues have ever used it. For these doctors the pitch is about medical heroism

Skeptical Experimenters are doctors who might try out something novel but do so in a gingerly fashion; these get a pitch about collaborative care.

Rule Bound Doctors are the ones who like to keep to Guidelines and other official advisories; these get a pitch based on guidelines.

The Conservative Majority are the majority of doctors who assume that what most of their colleagues are doing is likely to be right or at least safe. They like drug therapy to be uncomplicated – so the appeal to them may be about convenient formulations such as once a day dosing – leaving them time to focus on other aspects of care.

Not knowing what type you are is not a crime - the authors of this guideline don't know what type they are – but it is something to bear in mind.

**COULD MY JUDGEMENT BE AFFECTED IN ANY WAY BY A TARGET I SHOULD MEET?**

Every doctor today who wishes to offer good medical care is increasingly at risk of getting the sack as good care diverges systematically from officially endorsed healthcare inc. If you follow this guidance, you will for instance be at odds with a growing number of guidelines. But these are guidelines for diseases rather than guidance for people. We hope you will join us in trying to work out what to do for people and in reshaping medical practice to fit.

Until quite recently all drugs were regarded as poisons to be used with great care, ensuring that the risks of the illness that might be helped by treatment outweighed the unquestioned risks of the poison you were about to take. Company marketing has changed perceptions so that these chemicals are now regarded more like fertilizers to sprinkled liberally pretty well everywhere. This switch has been brought about in part by a marketing of fear and risk – you are told that left untreated the condition you have or your child has will lead to alcoholism, drug abuse, suicide, divorce, career failure and other problems. This is rarely true – for an increasing number of people the worry is that the treatment is more likely to produce this outcome than the illness.

DRAFT

## Appendix – Mood Stabilizers

Anticonvulsants	Trade Names
Carbamazepine	Tegretol
Divalproex	Depakote
Felbamate	Felbatol
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Oxcarbazepine	Trileptal
Pregabalin	Lyrica
Tiagabine	Gabitril
Topiramate	Topamax

### Antipsychotics commonly used or marketed for bipolar disorder

	Trade names
Chlorpromazine	Thorazine, Largactil
Perphenazine	Fentazin
Haloperidol	Serenace, Haldol
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Paliperidone	Invega
Ziprasidone	Geodon
Aripiprazole	Abilify