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# REBROADCAST #334: From pole to pole: New research into treating bipolar disorder

VOICEOVER

This is Up Close, the research talk show from the University of Melbourne, Australia.

SILA GENC

I'm Sila Genc. Thanks for joining us. Bipolar disorder is a complex group of psychiatric illnesses that burdens the lives of millions around the world. Treatments such as lithium have been longstanding in reducing the occurrences of manic or depressive episodes in individuals with bipolar disorder but these treatments come with a host of side effects that impact the day to day functioning of these individuals. Aside from the manic and/or depressive symptoms many people with bipolar experience, many of them have a host of cognitive deficits which have recently been targeted in new drug therapies. So how can we investigate these cognitive disturbances in the presence of this illness and is there the potential to simultaneously treat bipolar disorder and cognitive disturbances? Today on Up Close we speak to one of the leaders of bipolar disorder research, psychiatrist Professor Allan Young. Allan holds the Chair of Mood Disorders and is Director of the Centre for Affective Disorders in the Department of Psychological Medicine in the Institute of Psychiatry at King's College, London. Allan is in Melbourne as a guest of the University of Melbourne's Department of Psychiatry. Thanks for joining us, Allan.

ALLAN YOUNG

Thank you very much.

SILA GENC

Allan, let's start off with your primary area of research which is bipolar disorder. What is this complex range of illnesses and are there different types of bipolar

disorder?

ALLAN YOUNG

Bipolar disorder I guess is more properly called bipolar disorders because there is more than one type. It's a mood disorder which means that there is a disturbance in what we would call affect but there's also a number of other disturbances as well. Very broadly we talk about bipolar I disorder which encompasses episodes of mania where there's pathological elevated mood and at other times episodes of depression which can be pretty much the same as episodes of major depressive disorder. More complex however is the fact that these symptoms can occur together at the same time so as well as having a manic phase or a depressed phase you can have depressed symptoms when you're manic or manic symptoms when you're depressed. That's bipolar I disorder. Bipolar II disorder is where things get a good deal more blurry in terms of diagnosis. In bipolar II we have again major depressive episodes that are broadly similar to those of major depressive disorder but instead of having manic episodes we have hypomanic episodes which is not quite as severe as mania. These are often missed or not seen as being pathological and therefore bipolar II is often misdiagnosed or misascribed to be major depressive disorder. Then we have a whole range of what we call subsyndromal states. Some people call them the bipolar spectrum. This is where there are manic, hypomanic or depressive symptoms but not enough to amount to the diagnosis and these almost blend into what some people think of as being character traits like cyclothymia. So it's very, very complicated diagnostically. Not only do you have different categories but you have different phases and mixtures of phases within the category.

SILA GENC

So where are we right now in understanding the causative mechanisms of bipolar disorder? Are there genetic and environmental factors that determine if an individual's susceptible and you listed a few of the different types of bipolar disorder that exist, are there different causative mechanisms for the different types of bipolar disorder?

ALLAN YOUNG

Well we have seen a big advance in the genetics of psychiatric disorder over the last perhaps 15 years. We now know that the common severe psychiatric disorders like bipolar disorder and schizophrenia are not caused by one single gene that has a mistranslated protein and so on but rather they're due to a number of genes of small effect. I think the way to explain this is to say that the genetics is not like the genetics of say eye colour where you have blue or green or brown but rather the

genetics of height where there's multiples genes that interact although of course you do get these from your parents. Height runs in families, and so does bipolar disorder. Obviously for height there's an interaction with nutrition. At the turn of the century in the UK there was a very strong correlation between social class and height because basically people that were richer were better fed. We don't see that anymore but that's an example of how there's an interaction between environment and genes for something like height. The same is true with bipolar disorder so there's undoubtedly a genetic element. The genetic element appears to be pretty strong in bipolar disorder but it's not inevitable that if you've got bipolar disorder your kids will have. In actual fact your kids are more likely to have depression than to have straightforward bipolar disorder. In terms of the other factors that cause it, one of the big things is stress and we know that there's an excess of stressful life events before the first episode. Thereafter there doesn't seem to be an excess of stress but that's almost because I think the brain has become very hypersensitive to stress and can react in a stressful type way even when there isn't sufficient environmental stress. We know from measuring the physiological stress axis that this is out of control and people often have the hormonal levels of people that are acutely very stressed but long term and this is not good for the brain.

SILA GENC

Speaking of the brain, if we talk about bipolar disorder on a biological or even a structural level in the brain, is there some sudden change in the way the brain is actually organised when bipolar comes on or is it a gradual change or do we not even see changes in the brain?

ALLAN YOUNG

Well we do see changes in the brain. I think it's probably quite good to compare and contrast with schizophrenia. The reason for doing this is that in the 19<sup>th</sup> century the German psychiatrist Professor Emil Kraepelin who sort of set our thinking about all this really divided severe mental illness into what he called dementia praecox which is now schizophrenia and what he called manic-depressive illness which is now bipolar disorder. That's taking out things like Alzheimer's and it's notable that Alzheimer worked in the department of Professor Emil Kraepelin. So if we look at the two there is much more evidence for schizophrenia being what we call a neurodevelopmental disorder than bipolar. Even though there's genes contributing to bipolar disorder the manifestations of this in brain function aren't as evident early on as they are in schizophrenia. There's actually very good research about this from this part of the world and not from Australia I'm afraid to say but from New Zealand. In New Zealand there's a very famous study based in Dunedin where they did pretty simple pencil and paper tests on kids in the population at the age I think very young, four, seven, so on and so forth. They then followed these kids up in their 20s when you would expect some to become schizophrenic and some to have manifested

bipolar. When they looked back at the early pencil and paper tests the kids who became schizophrenic were actually performing significantly less well than their peers even very early on, even at the age of seven or four or whatever so they were significantly behind. That's one of the reasons we say this is neurodevelopmental because there's a different trajectory of brain development which manifests and performs in these types of tests. Interestingly, the kids who became bipolar, who got mania were actually performing better than average and this is something that we often see with bipolar disorder. Bipolar disorders often score a standard deviation so that's about 10 or 15 points better on things like IQ tests and cognitive function before the onset of illness. This is why there's a different trajectory between the two. This suggests that whatever is going on that's latest in the brain in bipolar disorder isn't manifesting the same way as it is with schizophrenia.

SILA GENC

Now Allan, this is obviously a very complex disorder. Is it just the brain that is affected in bipolar disorder? Are there any other areas of the body that are affected, that may manifest because of this disorder?

ALLAN YOUNG

Yes, absolutely correct. We know that people with severe mental illness and that's schizophrenia, bipolar disorder and severe depression die younger than the average age in the population and that's between 10 and 15 years. There's been a lot in the news about that happening with schizophrenia. It's certainly true for bipolar disorder as well and it's certainly true for depression. If we think about why these people die younger there is of course an early mortality due to suicide but the bulk of the deaths are from the common killers, the things that kill most people who die in their midlife, things like cancer and cardiovascular disease and so on and there's an excess of this. Now this is undoubtedly partly due to lifestyle factors and a big one is smoking which is excessively represented in these groups but there also may be some link at a more fundamental level. Certainly one of the things we've been very poor at is looking after the physical health of people with mental health issues. That really is a crying shame and most healthcare systems have been quite neglectful of these people because physical ill health issues and mental ill health issues tend to go together and they tend to be the most vulnerable people in society and they tend to be the people who are least good at accessing care. There's a whole parcel of issues there but certainly it doesn't just affect the brain, it affects the rest of the body and of course it affects the family and society and so on and so forth.

SILA GENC

You're listening to Up Close. Today we are talking about bipolar disorder with psychiatrist Professor Allan Young. I'm Sila Genc. Allan, let's talk about the current treatments of bipolar disorder. Lithium has been used as treatment for over 50 years. How does it actually work and is this currently the most effective treatment?

## ALLAN YOUNG

Well lithium certainly is one of the most effective treatments if used properly. It was of course reintroduced into medical practice by John Cade here in Melbourne in 1949. I think that remains one of the sort of landmark dates in the history of psychiatry. It had been of course for many years before that considered to be something which did have effects on mood and of course it was often added to food stuffs and so on but it was banned by the US FDA for that in the 1940s. Lithium is an element, it's not a drug that was made or manufactured by anyone and therefore it's never had the same degree of marketing or so on that some of the other drugs have had because it's impossible to make much of a profit out of lithium. I think this is a great shame because lithium is very important. We're still discovering more and more about it. Now when lithium came in it was championed by psychiatrists like Cade and Morgens Schou in Denmark and so on. It took a long time for it to be accepted and there were people who were very harshly critical of it. In my own institution Professor Michael Shepherd called it a toxic placebo and it was thought for many years that that's what it was. It certainly is toxic in terms of its side effects if taken at too high a dose but it's certainly not a placebo. It's now quite clear that lithium is an effective treatment and if you take it it reduces the risk of having another episode principally of mania, perhaps not so strongly of depression. Also intriguingly it reduces the risk of suicide and this is one of the few treatments that we have which has been shown quite convincingly to reduce the risk of suicide in people that take it. There are side effects with lithium, particularly concerning effects on the kidney and this is because of its effect on the sodium channel. It initially causes polyuria so an excess production of the volume of urine and it is associated long term if taken at the wrong dose with renal failure. However, it's notable that there's a recent paper been published from Sweden where they instituted very careful monitoring a number of decades ago and since then in the whole country have not had one case of lithium induced renal failure. As to how it works that's still a bit of a mystery but we do have some pointers. The first thing to say is that none of the funding agencies in North America or Europe are particularly keen on supporting research into lithium which I think is rather bamboozling given it's such an interesting and fundamental treatment. However, we do now know that it has effects on brain dopamine for example. We also know that it has effects on neurogenesis and may increase the volume of grey matter in the brain. There's also an intriguing literature which has arisen in the past decade or so about environmental lithium. Lithium of course is an element which occurs in environments and salts are present in the water that we drink and are concentrated in foodstuff and so on. There was an initial paper from Texas that showed that higher environmental levels of lithium were associated with lower rates

of suicide just as for example the therapeutic studies show that therapeutic lithium reduces suicide and lower rates of things like murders, et cetera, et cetera. This was dismissed because many people thought that the level of environmental lithium which is a lot lower obviously than taking it as a medicine, wouldn't really have any effect on the brain. This finding, particularly the effect on suicide at a population level, has been shown in Japan, Austria and so on and large, large studies. So there does seem to be something fundamental going on with lithium in the brain and the environmental lithium is a way that this is manifest. The other intriguing thing about lithium is the literature that lithium may prevent dementia. Of course one of the things that we are searching for everywhere is a drug to prevent or to cure dementia and most of the research efforts have come up very short on this. One of the neurochemical pathways which is normal in dementia, in Alzheimer's disease is modulated by lithium and my colleague in England, Professor Simon Lovestone who's now at Oxford University has done much work on this over the years. There is certainly a suggestion that if you take low dose lithium this may prevent onset of dementia. This hasn't been done in a large definitive trial but there's at least one small trial in South America that suggests this. I think lithium has a panoply of different effects. It's always going to have the problem of having what we call a narrow therapeutic index. The difference between taking a therapeutic dose and a toxic dose is pretty narrow. Monitoring and care is essential but if used correctly it can be very beneficial.

SILA GENC

If we look at the drug lithium and other drugs that can be used for bipolar disorder, are they actually modifying the illness? I know you mentioned that grey matter can change in the brain but if individuals with bipolar stop taking the medication are they just as susceptible for having a manic or depressive episode?

ALLAN YOUNG

Well in actual fact if you stop taking your medicine you have a rebound effect where you're actually more likely to get an episode of illness and this is something that's particularly true for lithium but is also true for I think all of the medicines which are used in bipolar disorder so this is true for the anticonvulsant mood stabilizers, the so-called antipsychotics which are used and even the anti-depressants. We did a very large study in the north of England where we looked at people who had stopped their medication but there was no indication that they were ill at the time that they stopped and if you stop your medication, most of the classes, lithium, the anticonvulsants, antipsychotics there's an 80 per cent chance of relapse within the next three months. We didn't think this was because they were stopping it because of the early stage of relapse. If you stop anti-depressants and anti-depressants are a very contentious area in bipolar disorder because there's not much evidence that they're actually helpful for the depressed pool but if you stop the anti-depressants there's an

increased risk of relapsing into depression. One of the key determinants of a good outcome in bipolar disorder is adherence to medication and that's something which psychologically can be difficult to accept. It's a bit like someone with diabetes. You've got to take the insulin or the regime of diabetic medications to improve your long term outcome but there's no immediate gain. The same is true with bipolar disorder. You've got to take these medicines. Sometimes they give you side effects which you don't like but it's at the effect of a long term gain rather than an immediate gain. Psychologically that can be very difficult and people require sometimes a lot of therapy to get them to accept that or to work through the issues.

SILA GENC

I guess when people with bipolar are not having an episode or when they're not in a manic or depressive state presumably because they're on medication, do they function normally as though they don't have the condition and hence feel they don't need to take the medication?

ALLAN YOUNG

There is a range of outcomes with bipolar disorder and it's important to note that some people have a very, very good outcome. I often get patients coming to see me who have read information on the internet and the information is very gloomy. They often arrive in my clinic I won't say feeling suicidal but they feel very gloomy because of all the information they've read. Some patients have a very good outcome. There may be a subgroup who don't require medication. I think that's contentious but there's certainly a fairly large percentage who do well with monotherapy lithium or some other medication. It's the more complex and treatment resistant cases that we tend to see more of and therefore they tend to occupy a larger part of our mental space as it were because we see more of these people but if you look in the community there's undoubtedly some people who do well and even the most complex and treatment resistant cases in my experience can do well and can recover lots of function and especially cognitive function I think can be recovered.

SILA GENC

I'm Sila Genc and on Up Close this episode we're talking about bipolar disorder with research psychiatrist Professor Allan Young. Allan, a particular interest of yours is the impact of bipolar on cognition. What kind of cognitive deficits do you typically observe in individuals with bipolar disorder?

ALLAN YOUNG

Well mood disorders which is depression and bipolar disorder both have cognitive deficits and when we talk about cognitive deficits we're talking about things like attention, working memory and so on and so forth. These are things that we tend to take for granted. It's only been in the last few decades that we've actually had tests such as those developed in Cambridge by Professor Trevor Robbins and Professor Barbara Sahakian which have captured things like executive function correctly. If we look at depression there's impairments which seem to resolve with the episode of depression. If we look at bipolar disorder there's similar impairments. These aren't quite as marked as they are in schizophrenia but they do tend to get worse with each subsequent episode and they're across the whole range of domains -- attention, working memory, verbal fluency and so on and so forth. We find that if people recover symptomatically and stay well for a prolonged period of time they can recover a great deal of cognitive function, perhaps all of it but that's not something that we've fully established yet.

SILA GENC

Do we know if these cognitive deficits are associated with the disorder itself or a result of the medication that's typically prescribed for bipolar?

ALLAN YOUNG

Well we don't think they're a result of the medication. It's very difficult to ascertain this because we were interested in the cognitive deficits in depression and we did a study in people who were drug free with depression. It's actually very difficult to get people who've never been on treatment who are bipolar, at least in a country like the UK or Australia. We looked at this question with colleagues in India and we were able to look at people freshly diagnosed and never been treated with medication and indeed people who'd had episode that hadn't been treated and then recovered and they show the same pattern of cognitive deficits on these computerised tests. We also see similar patterns although watered down in relatives. Now that's a bit more complicated. That may be because there's been some sub-threshold illness in relatives but we do think that this isn't due to medication. Indeed one might expect that some of the medications I mentioned, the effect of lithium on grey matter might improve aspects of cognitive functioning. I think the medication's a bit of a red herring here in terms of the effects on cognition. There are of course other things associated with bipolar disorder that impair cognition. One in particular is alcohol and substance misuse. This is a very common comorbidity for bipolar disorder. Somewhere between 40 and 70 per cent of people with bipolar disorder will have an alcohol or substance misuse problem at some point and obviously can interfere with your cognition as well.

SILA GENC

Allan, tell us a bit more about the course of the cognitive deficits?

ALLAN YOUNG

Well the first thing to say about that is that at the first episode people with bipolar disorder don't appear to perform much worse than the general population. Indeed obviously in some things they're brighter than average. I mentioned the fact that they've got on average a higher IQ score and this is in contrast to people with schizophrenia where the cognitive deficits are a very early feature of the disorder. However, what seems to happen in bipolar disorder is that each episode appears to produce decrements in your cognitive functioning and that's been shown in studies in North America, Europe, Australia and we actually showed it recently in a study in China, that it's the episodes of illness that cause an increased impairment. There's a couple of points about this that should be made. One of course is that each episode of illness may be causing some degree of damage to the brain or you may be selecting a group who have got a highly recurrent illness who are actually going to do worse anyway. However, the argument's quite clear that if you can reduce relapse rates, reduce the number of episodes of illness you can actually reduce the occurrence of the cognitive deficits. I don't think this detracts from my other point about people with prolonged euthymia actually having a return of some cognitive function. Even if you've had a number of episodes I think the brain is still quite plastic. The adult human brain is much more plastic than we believed 20 or 30 years ago and I think the capacity for recovery is still there.

SILA GENC

Allan, there are many clinical trials around the world aiming to address these cognitive deficits and you yourself were involved in many of these. Could you tell us a bit more about the treatments currently being trialled and how promising the outcomes have been so far?

ALLAN YOUNG

I guess you could divide them broadly into two. There's a group of what we call cognitive remediation type studies which are essentially brain gym training if I can use that analogy. My colleague in the Institute of Psychiatry, Professor Til Wykes developed this for schizophrenia. I did mention that schizophrenia has more of a neurodevelopmental aspect than bipolar disorder and therefore you might expect any cognitive remediation, which is essentially practising your cognitive tasks, your cognitive skills to be less effective than bipolar disorder. We are using this in bipolar

disorder. There isn't a great deal of literature there yet but certainly it's something that we hope to follow up. There's similar work going on in places like Barcelona except their approach is a bit broader. They talk about functional remediation and building life skills and so on as well. Then there's medication. As we've just mentioned we are certainly concerned about medication making cognitive deficits worse but we've also done work over the past 15 years or so looking at drugs which block stress hormones. This goes back to work I did in the '90s where I was interested in what might cause the cognitive impairments in mood disorders and we gave normal healthy volunteers a week of high dose steroids producing a level similar to that that you'd find in bipolar disorder for example. This produced deficits, reversible deficits I should say, in aspects of cognitive function, particularly things like spatial working memory which is what you use when you find your parked car in the multistorey car park. That was a particular marker for us and we've done studies where we've used drugs which have blocked the stress hormones and they've improved cognitive function, particularly spatial working memory which I think is just really a barometer for cognitive function rather than being a specific effect. I think there's a possibility of medication. There's also the possibility of cognitive remediation and ideally what one would like to do is to do studies where you combine them both to give the optimal package. I also think that people that stay well for a prolonged period can recover an awful lot of cognitive function. People with bipolar disorder are often very talented bright people who are very accomplished. The cognitive deficits are very subtle but they feel them quite deeply because they've lost an ability that they took for granted. We've certainly seen people who have stayed well for two or three years who've actually recovered a great deal of cognitive function objectively verified by our tests. I think this is something to say to people with bipolar disorder, that the brain's plastic and there's a good deal of scope for recovery but it lags behind a symptomatic recovery. You deal with the depression or the mania first, then there may be some residual symptoms and then there may be an improvement which follows in cognitive function.

SILA GENC

Last thing Allan, how close do you think we are in terms of finding a treatment that will lead to typical or normal functioning individuals with bipolar disorder?

ALLAN YOUNG

Well I actually think we have treatments that can do that at the moment. What we're not very good at is actually applying these treatments. I think there's a great argument for actually first of all improving diagnosis. That's the number one thing that people with bipolar disorder want. People with bipolar disorder have a desire for accurate diagnosis because typically they can go for 10 years and they've been told that they've got depression or substance abuse or an anxiety disorder or whatever and in actual fact it's actually bipolar disorder. If there's early diagnosis and then

there's early appropriate treatment with combined medication and psychological treatments and as I've said, one of the biggest aspects of the psychological treatments is dealing with the denial and acceptance of the illness and there's things like psycho education and so on and we do use every variety of psychological treatment, I think you can make outcomes an awful lot better. I think if we did really want to focus on trying to get a better treatment we'd really want to deconstruct what lithium's doing but this is why it's very frustrating that it's very difficult to get governmental research grants to research lithium because people somehow think it's passé but in actual fact it's like saying you can understand diabetes without understanding insulin.

SILA GENC

Allan, thank you very much for being our guest on Up Close today and talking with us about bipolar disorder.

ALLAN YOUNG

Thank you.

SILA GENC

That was Professor Allan Young, the Chair of Mood Disorders and Director of the Centre for Affective Disorders in the Department of Psychological Medicine in the Institute of Psychiatry at King's College, London. Relevant links, a full transcript and more information on this episode can be found on our website. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 15 December 2014. Producers for this episode were Eric van Bommel, Kelvin Param and me, Sila Genc. Audio engineering by Gavin Nebauer. Up Close is created by Eric van Bommel and Kelvin Param. Until next time, good bye.

VOICEOVER

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