

## It's all in the genes!

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**Singapore:** WHO estimates that globally, nearly 350 million people suffer from depression. As explained by the health governing bodies, depression is a common illness worldwide and is different from mood fluctuations and short responses to daily challenges in life. Affecting more women than men, depression is considered as a major cause of disability, and a major contributor to global disease burden. When long-lasting and with moderate or severe intensity, depression may become a serious health condition and can cause the affected person to suffer greatly and function poorly at work, at school and in the family. At its worst, depression can lead to suicide. Over 800 000 people die due to suicide every year. Suicide is the second leading cause of death in 15-29-year-olds. The burden of depression and other mental health conditions is on the rise globally. A World Health Assembly resolution passed in May 2013 has called for a comprehensive, coordinated response to mental disorders at country level.

The major issue with battling depression is the stigma associated with it. Although there are known, effective treatments for depression, fewer than half of those affected in the world (in many countries, fewer than 10 percent) receive such treatments. Barriers to effective care include a lack of resources, lack of trained health care providers, and social stigma associated with mental disorders. Along with this, another major barrier to effective care is inaccurate assessment and inability to decide the right dosage of medicine for a particular patient. In countries of all income levels, people who are depressed are often not correctly diagnosed, and others who do not have the disorder are too often misdiagnosed and not prescribed the correct dose of medication.

A group of young specialists from Australia have set out to resolve these challenges through their innovative start-up, CNS Dose that harnesses the power of genetics to tailor and customize dosages of anti-depressants as per patient needs, to maximize the effect of medication and to minimize the errors. The CNSDose product was developed over the last 10 years by Associate Professor Dr Ajeet B Singh, a practicing psychiatrist and globally-recognized pharmacogenetics expert, CEO and Founder of CNSDose.

"After my first year in practice as a psychiatrist it was very apparent to me that much of the prescribing in psychiatry is on a trial and error basis," explained Dr Singh, "It takes nearly a month to judge if a medication is starting to work at a particular dose and patients can spend several months to years in a trial and error prescribing process. It's incredibly inefficient and delays recovery. Often patients get frustrated with the process and give up on care. Back in 2006 I had the idea that perhaps genetics may help reduce the trial and error prescribing. In 2012 I established a private company to develop an antidepressant guidance system. In 2015, I was joined by two co-founders - Mr Campbell Walshe MBA and Dr Harris Eyre MD PhD to progress the startup. Mr Campbell brings commercial development experience and Dr Eyre brings added medical and academic firepower to the team - being a Fulbright scholar at UCLA in 2015 and recently completing a neuroscience PhD. It's now very much a group effort."

CNS Dose's technology utilizes genomic testing to determine an individual's ability to metabolize antidepressants, thus improving the response to these drugs. Patients send a saliva sample and the technology analyzes various genetic variants of liver enzymes (involved in metabolising antidepressants) and genetic variants in the blood brain barrier. The results are then inputted by the lab into the CNSDose secure cloud server that generates a simple to understand medication guidance report for the doctor. The report stratifies 20 commonly used antidepressants into high, medium and low dose groups that help guide the doctor.

"The report has been shown to double recovery from depression compared to traditional trial and error prescribing in our clinical trial," Dr Singh, highlighted. "The finding was independently replicated by tenure-track academics - confirming the initial finding, with the method over 85 percent accurate. We have an Asian bespoke version of the test that includes gene variants more commonly found in Asian patients. All medication decisions are made by the treating doctor and the report is an added piece of information to support that decision making process."

Though the company currently has tested the technology only for depression, Dr Singh believes that the unique test should apply to a variety of brain disorders and other psychiatric medications, like epilepsy and dementia. Moving ahead the company is also planning to explore the test to other indications and focus on R&D to further enhance our technology and extend its indication to other medication classes.

The company plans to start sales in the USA this October, with their US lab affiliate. Confident that their technology will create waves in the market, CNS Dose aims to expand rapidly and is keen to grow into Asia and conduct a clinical trial in Asia. "There is scope for CNSDose to be a platform technology. The leveraged business model of partnering with affiliated labs enables rapid global scaling, said Dr Singh, "I see CNSDose becoming a global leader in the space, driving R&D to move from the current '1 megapixel' camera stage to 10 megapixels of genomic resolution to help guide prescribing of Central Nervous System (CNS) medications. This is how the report got its name - CNSDose."

Speaking about the challenges, Dr Singh said, "There is competition. At present there are two other companies - both in the US - with clinical trial evidence of a genetic guidance report helping in care of depression. But neither has a positive RCT - only having less robust clinical trial data. Also, neither of these companies has included the Blood brain barrier genetics in their reports - a key hurdle to medication entry to the brain. So I am confident we have a technological and evidence edge at this stage. Finally, both these US companies operate out of a single lab. Our leveraged business model of partnering with labs globally gives us a rapid scalability edge. For these reasons I think we're in a strong position. My instincts tell me the biggest challenge we will face is managing rapid growth."

Excerpts from the Interview:

1.How important is a person's genetics in deciding the right amount of medicine?

For some patients average doses of medications work fine. But for other patients their metabolism is such that average dose can lead to side effects or toxicity, and in others their metabolism means average doses are not strong enough for the medication to reach the brain - preventing the medication from ever having a chance to work. For such patients genetics can be a key clue to determining which medication is the best fit for them. Most medications are tested in Caucasians, with the appropriateness of the dose being assumed to apply to Asians. But genetic profile can be different between ethnic groups. We think that genetically guided prescribing will be especially relevant in an Asian setting. We're still at an early stage in precision medicine, and it is likely in years to come the accuracy of the testing will improve further still. I think at the moment it's a bit like a 1 megapixel camera - in time the resolution of genetic reports will improve further and help guide doctors even more. It's an exciting time for progress in reducing trial and error prescribing.

2.Please highlight the uniqueness of this test and what difference it can create in medical industry?

The CNSDose report has the first positive randomized controlled trial (RCT) in the world. This type of study is considered the most rigorous robust form of clinical trial in medicine. The replication of the finding by independent academics helps further confirm and elevate the level of evidence for the CNSDose report. The clinical trials have been submitted to peer-reviewed journals, the RCT published in late 2015, the replication study in submission at present. Peer-review is essential - independent experts in the area review the study before it is published in a scientific journal. This acts as a due diligence process. We hope to conduct further clinical trials on the report to further enhance the evidence base. Robust published peer-reviewed clinical utility evidence is essential.

3.Despite much medical advancement, battling depression is still a major issue, especially in urban areas. What in your opinion could be a reason?

I think stigma is a big issue. Everyone gets sad from time to time, but major depression is much more than sadness. It's a persisting state of very low mood and drive that can be crippling. Some people fear seeking help as they fear being judged as "weak". In countries like Australia stigma has reduced greatly with government funded public awareness campaigns. Governments are increasingly aware that tackling depression not only helps save lives, but also improves economic productivity, and reduces various health care costs. For these reasons more educational campaigns on depression are being funded, but it takes time for stigma to reduce. In Asia stigma remains high - stopping many from getting help. Beyond stigma, I think social isolation from urbanisation is a key factor too. Asia in particular has seen very rapid urbanisation in recent years. I think this rapid urbanisation will be a key social factor - unfortunately triggering many cases of depression in Asia. Economic uncertainty only adds to the stress load and risk of depression. I think these factors are coming together and underpinning a growing burden from depression in Asia.

4.The silence about mental health issues is dangerous. In your opinion, how is the scenario in Asia?

I think it's a missed opportunity. Tackling depression not only improves lives, it improves the economy. Many studies have demonstrated that depression worsens productivity. I think as Asia develops a Western profile of illness during this era of rapid economic development and urbanisation, it will also see a spike in cases of major depression. The social and economic impacts will be enormous. I think astute Asian governments are aware of this, but have the dilemma of there being only a very limited mental health workforce available to them. Scalable technological solutions - like genetically guided antidepressants - offers some hope. In effect the family doctor could be able to prescribe antidepressants more effectively, enabling better treatment outcomes sooner. This may also have the added advantage of people discretely obtaining effective care from their family doctor. This helps reduce the impact of the stigma factor - which sometimes prevents people seeing a psychiatrist or attending a mental health service. But I am optimistic. I think in the Asian century one of the next waves of Asian development will be tackling depression stigma and enhancing help-seeking.

5.Please share some major achievements and key initiatives planned by CNS Dose for the future

We were fortunate to win The University of Melbourne accelerator program competition called 'MAP' earlier this year. This is the top rated startup accelerator in the country, and highly competitive with both Australian and international entrants. We were also fortunate to have the immediate former Trade Minister of Australia - Mr Andrew Robb AO - agree to chair our advisor board. He brings immense trade contacts and has also personally experienced the perils of trial and error antidepressant prescribing. He has been joined on our Advisory Board by Professor John Tiller. John is the immediate past head of department of Psychiatry at The University of Melbourne and Emeritus Professor of Psychiatry. He is impressed with our technology and evidence base. Finally, we were also recently fortunate to attract Mr Mark Heinemeyer - a successful

serial medtech entrepreneur from Los Angeles. The strength of the advisory board along with the Melbourne University accelerator program have been great initial boosts for us. This along with our oversubscribed seed round have helped make us feel very bullish about the future of CNSDose. Successful test of traction in the US later this year is the next key step for us. We feel we will then be ready to rapidly ramp up the company via a series A capital raising round. Our mission is to reduce the global burden of depression through genetics.