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impressions

A scientific symposium in Hong Kong

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Editorial

Welcome to **impressions**, your guide to important news and progress in the care of patients with depression and related disorders. Inside, we **highlight** Dr Philip John, one of India's leading psychiatrists, who shares his passion not only for neuropsychiatry and developmental disorders in children but also for the unique properties of SSRI and sigma-1 receptor agonist fluvoxamine. **Update** reviews a recent international symposium at the XXVII CINP Congress held in Hong Kong and focused on the use of sigma-1 receptors to improve patient outcomes in depression. **Memory** looks at the life of Rosemary Clooney, a gifted singer who appeared with Bing Crosby and Danny Kaye in the film White Christmas, but whose career was disrupted midstream by bipolar disorder. In **Scientifically speaking**, Professor Kenji Hashimoto discusses the emerging clinical implications of fluvoxamine that are potentially based on its sigma-1 receptor agonist properties. Your feedback, contributions and suggestions are always welcome using the email contact address below.

Dr Cláudio Sandner

Publication

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Impressions of Dr Phillip John

Dr Philip John is a senior consultant in psychiatry with a professional standing of more than a quarter of a century in Cochin, India and in Sharjah, United Arab Emirates. After graduating in medicine he trained and obtained his MD degree in psychiatry from National Institute of Mental Health and Neuro-Sciences, Bangalore. Heading the Psychiatry Division in the largest private sector tertiary referral hospital then in Kerala, he endeavored primarily to move psychiatry into the mainstream of medicine, enabling its de-stigmatization among fellow physicians. Following a decade of consultation-liaison psychiatry, he pioneered the open office-practice that facilitated the collaboration between medical specialties and psychiatry. Dr Philip John has worked hard to practice psychiatry as the application of basic neurosciences to man's day-to-day problems. He pioneers many unique, patient-centered and fresh approaches in psychiatry. He was conferred the Vishakha Oration Award by the Indian Psychiatric Society for outstanding contribution to psychiatry. Dr John is a familiar faculty member across the country for CMEs and conferences.

In your clinical practice in India and overseas, how frequently do you use the SSRI fluvoxamine?

In Adult Psychiatry practice, I encounter difficult and resistant depressive, obsessive and psychotic disorders where I use fluvoxamine. Child Division work is focused on learning, developmental and behavioral disorders. I am often surprised by the number of fluvoxamine prescriptions I write. I am a cautious physician and these increasing prescriptions are solely the consequence of compelling feedback by the parents of these children about the unique and sometimes dramatic effects of fluvoxamine. But we need more evidence-based studies to substantiate these clinical experiences.

What set you off with the initial prescriptions of fluvoxamine?

Two things. Based on the multidisciplinary evaluation of more than 5,000 children, we have proposed a robust 'spectrum construct' with a left brain bias for all specific developmental disorders.[1] We are convinced that obsessive disorders and obsessive spectrum disorders fall under a developmental rubric; obsessive disorders in children are distinct and different from adult obsessive disorders and are developmental in origin. We began using fluvoxamine for OCD in children, initially because of its authorization for use above eight years of age. As months passed, parents would report the amelioration of a plethora of co-existing symptoms. This feedback set us thinking on a broader base for appliication of this SSRI – if many of these symptoms improved in one go, then we need to think of one drug cutting across many functional neural domains and all these domains together may be in one axis of developmental origin. This axis of specific developmental disorders and obsessive /obsessive spectrum symptoms, pervasive developmental disorders, autism and the resistance to 'change' with its consequent behavior, cognitive deficits of attention and language, especially expressive language etc. are all explicable from a background of neuronal maturation, neuroplasticity and the concept of 'connectivity'. If neuroplasticity improves cognitive functions by neuronal repair to neurodegenerated brain (as in major psychiatric illnesses), we now discern that fluvoxamine can transform neuronal functioning in the deficient brains of developmental disorder children through metamorphosing 'connectivity'. Our 'spectrum construct' for all (high-functioning) developmental disorders, and the application of neuroplasticity to these developmental disorders are two things that set us off in this emerging strategy.

For which disorders you find fluvoxamine most beneficial?

An array of irksome symptoms. Broadly, obsessive disorder in children, including obsessive traits that disturb personal or interpersonal comfort in the family or school. Neuronal remodeling using an appropriate SSRI makes it easy for these children to tolerate the stress of change, to tolerate frustration and criticism. Even attention span and concentration improve with regulation of obsessive and anticipatory anxiety. Annoying symptoms like nail biting, skin picking, multiple specific phobias, kleptomania etc. seem to fade away on their own. Flexibility and adaptation to change is a great transformation. Many parents tell us about the positive changes in meta-cognition. Language becomes more meaningful in its expression and narration, possibly an outcome of greater neuronal connectivity, on long-term use of fluvoxamine. Potentiation of neurotrophic factor signaling processes which improves neuroplasticity to enable neuronal remodeling of the brain must be core to these changes. The improvement appears to be proportional to the non-pharmacological, academic, language, and behavioral strategies that are employed with each child.[2]

Would you consider some other specific indications for fluvoxamine?

In behavioral problems consequent to the obsessive aspect of autism spectrum disorders, (especially high-functioning), in Asperger's Syndrome, in obsessive disorder with tics in children, in obsessive spectrum disorders (including kleptomania, trichotillomania, and pyromania), in childhood IBS and enuresis, children with body dysmorphia or olfactory reference, the list may go on. In adults, it is used in depression with psychosis, obsessions with insight loss, schizo-obsessive psychosis, schizo-affective psychosis where mood symptoms are masked by the psychotic symptoms, early cases of degenerative dementia etc. I do not wish to appear to advocate fluvoxamine as a panacea for all troubles. We need evidence. In all these disorders I always combine the psychopharmacological approach with multipronged non-pharmacological and behavioral strategies in the hierarchical multidisciplinary framework of my clinical work.

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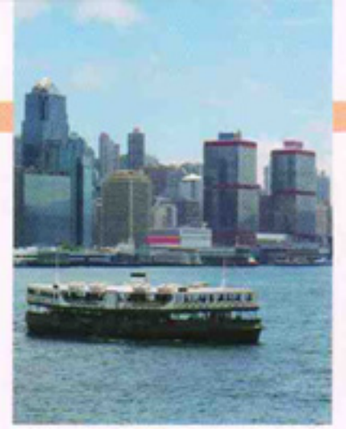
Disclaimer:
This text reflects the main points and views made by the interviewee.

Fluvoxamine is approved in the treatment of major depression in adults and of obsessive-compulsive disorder in children and adults. In Japan Fluvoxamine is also approved for the treatment of social anxiety disorder.



Sigma-1 receptors in depression:

towards improved patient outcomes

An international symposium at the XXVII CINP Congress held in Hong Kong on June 8th, 2010.

The focus of the symposium was on the appropriate use of selective serotonine reuptake inhibitors such as fluvoxamine to improve outcomes in patients with major depressive disorder MDD.

It is increasingly recognised that sigma-1 receptors mediate several clinically important effects of certain antidepressants, in particular fluvoxamine. Discovered in 1976 and cloned in 1996, sigma receptors, are dynamic endoplasmic reticulum proteins that regulate the glutamatergic system via the modulation of the NMDA receptors in the brain. The activation of sigma-1 receptors may contribute to the proper functioning of active ion channels and signal transductions essential for physiological functions of neurons (e.g. release of a number of neurotransmitters including DA, 5-HT, NE, ACh). The activation of sigma-1 receptors may also induce potentiation of neurotrophic factor signalling, cellular differentiation and cell survival. Chronic sigma-1 receptor activation also contributes to the formation and recomposition of membrane lipid rafts, with direct consequences for neuroplasticity.[1-6]

The internationally renowned faculty included Professor Kenji Hashimoto (Japan), who discussed the clinical implications of using fluvoxamine based on its sigma-1 receptor agonist properties, and Professor Alessandro Serretti (Italy) who discussed whether efficacy and tolerability considerations are enough when selecting the right SSRI.

Individualizing therapy is important in order to optimize clinical outcomes. Therefore, it is important to consider which type of patient would benefit most from which agent. Given that clinically important differences exist between the SSRIs, the question of which to prescribe might be viewed as a clinical dilemma. Each agent has specific features that can be important when tailoring therapy to each individual patient. This is a reflection of specific secondary pharmacodynamic properties and adverse behavioural effects of each agent. In this regard, certain specific properties of fluvoxamine may help physicians to decide which are the most appropriate patients to receive this SSRI.

The faculty concluded that, aside from being a well known efficacious treatment of depression, fluvoxamine has proven to be a particularly effective treatment in many subgroups of patients, including delusional depression, the elderly and when trying to minimise the incidence of sexual dysfunction.

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Hong Kong

Rosemary Clooney in her latest months

Rosemary Clooney,

a career disrupted by bipolar disorder

Rosemary Clooney was a gifted American singer whose career was disrupted midstream by bipolar disorder. Her family history contains some elements common for people with manic depression.

She and her sister Betty were left behind when their mother went off to be married a second time, taking only their brother Nick with her; their alcoholic father eventually abandoned the young sisters. The two girls were living in poverty when they won a contest and earned a regular job singing on the radio in 1945.

The Clooney Sisters were hired by bandleader Tony Pastor two years later, and when Betty decided to return to their home city of Cincinnati for a quieter life, Rosemary went on alone. In 1951 she recorded "Come on-a My House," a song she hated, and it made her a star.

In 1953 Rosemary Clooney married actor Jose Ferrer (their oldest son, Miguel Ferrer, is a TV star). Co-hosting a daily morning radio show with Bing Crosby led to her being cast with him and Danny Kaye in the film White Christmas (1954). She also worked in television and other films in the 1950s, while having four more children by 1960. Trying to maintain both family and strenuous career demands began to take its toll on her, and she became addicted to tranquilizers and sleeping pills. Her marriage crumbled; she and Ferrer were divorced in 1961, reconciled, and divorced again in 1967.

In 1968, after the trauma of being present when her good friend Robert F. Kennedy was assassinated, she suffered a raging manic episode onstage and soon was hospitalized for psychiatric care, at times in a double-locked ward because she had become so violent. Her therapy continued for several years. By the time she was seen by the viewing public again, she had gained a great deal of weight which stayed with her for the rest of her life - but her voice still had the same warm, mellow sound.

Her career was reborn after she appeared in a benefit with Bing Crosby in 1976. An autobiography, This for Remembrance, which describes her illness, was published in 1977. She continued to work for many more years. You may have seen her two performances with nephew George Clooney on the television series ER. In 1996 she married Dante DiPaolo, a dancer whom she had dated before marrying Ferrer.

Rosemary Clooney died Saturday, June 29th, 2002 after a struggle with lung cancer. She was 74.

Rosemary Clooney in former times

Further reading

1. http://bipolar.about.com/cs/celebs/a/rosemaryclooney.htm

Scientifically speaking

The importance of sigma-1 receptors in depression and cognition

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Disclaimer:
The following text reflects the main points and views made by the author.

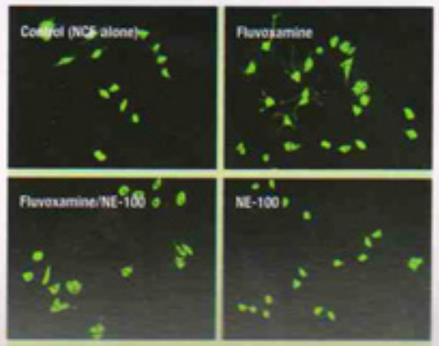
The selective serotonin reuptake inhibitor (SSRI) fluvoxamine has the highest affinity for the sigma-1 receptor in rat brain compared with various other antidepressants tested **(Table 1)**.1 However, while fluvoxamine is a sigma-1 agonist, sertraline, which also has a relatively high affinity for sigma-1 receptors, acts as an antagonist.[2] This difference has important implications for their respective clinical effects.

Fluvoxamine, but not sertraline or paroxetine, potentiates nerve growth factors (NGF)-induced neurite outgrowth in PC12 cells; an effect antagonised by the selective sigma-1 receptor antagonist NE-100. The influence of fluvoxamine on neurite outgrowth using MAP-2 immunocytochemistry (a neuronal marker; **Figure 1**) suggest a potential sigma-1 receptor-mediated involvement of fluvoxamine in mechanisms of neuroplasticity and neuronal remodelling.[3]

Table 1. In vitro affinity of various agents for rat sigma-1 binding sites

Drug	Ki (nM)		Ki ratio
SSRIs	**Sigma-1**	**Sigma-2**	**Sigma-2/Sigma-1**
Fluvoxamine	36	8,439	234
Sertraline	57	5,297	93
S(+)Fluoxetine	120	5480	46
(±)Fluoxetine	240	16,100	68
Citalopram	292	5,410	19
Paroxetine	1,893	22,870	12
Tricyclic antidepressants			
Imipramine	343	2,107	6
Desipramine	1,987	11,430	6

Figure 1. Fluvoxamine stimulated NGF-induced neurite outgrowth in PC12 cells[3]



Recent evidence indicates that the sigma-1 receptor is a Ca2+-sensitive and ligand-operated receptor chaperone at mitochondrion-associated endoplasmic reticulum (ER) membrane.4 The communication between the ER and mitochondrion is believed to be critical for bioenergetics and cellular survival. Receptor chaperone **(Figure 2)** is a relatively novel concept in pharmacology and explains how the interaction between the sigma-1 receptor and BiP (a chaperone immunoglobulin binding protein) or a synthetic agent leads to either inhibition (as with sertraline) or activation (as with fluvoxamine) of the receptor.

Cognitive impairment is a primary feature of patients with major depressive disorder (MDD) and is characterised by stress-induced neural atrophy, particularly in the hippocampus, amygdala and prefrontal cortex. Sigma-1 receptors are abundant in areas affected by depression/stress-induced cerebral atrophy and their ligands may consequently promote neurogenesis and initiate adaptive neural plasticity as a protection/reaction to stress. Fluvoxamine has shown ameliorating effects in psychosis, depression, stress, anxiety, obsessive-compulsive disorder (OCD) and aggression and has been shown to improve or restore cognitive impairments.[4,5] For example, in an animal model, phencyclidine (PCP)-induced cognitive defects were ameliorated by subchronic administration of fluvoxamine, but not by paroxetine or sertraline **(Figure 3)**.[5,6]

In recent case reports, fluvoxamine added to standard antipsychotic therapy improved cognitive impairments and reduced negative symptoms in patients with schizophrenia and, separately, fluvoxamine helped to improve delirium and sleep disturbance in patients with Alzheimer's disease.[7,8] These effects are supported by the observation of high (and dose-dependent) occupancy of sigma-1 receptors in living human brain following the administration of therapeutic doses of fluvoxamine (50-200 mg) to healthy male volunteers **(Figure 4)**.[9]

There is increasing interest in the use of fluvoxamine for the treatment of psychotic major depression, based on a series of clinical studies[10,11] and case reports.[12,13] The efficacy of fluvoxamine in psychotic major depression may also be related to its unique property of high affinity for the sigma-1 receptor.[14] In a recent case study involving a 36-year-old woman with psychotic depression refractory to antipsychotic therapy, the symptoms of depression and psychosis improved after fluvoxamine monotherapy. However, three years later, a switch to sertraline from fluvoxamine dramatically worsened the psychotic symptoms. A switch back to fluvoxamine from sertraline improved these symptoms one week after fluvoxamine treatment.

Fluvoxamine is a unique SSRI with sigma-1 receptor agonism playing a potentially important role in its efficacy profile. Further clinical studies are required to confirm these observations and provide an evidenced base for a clinical role of fluvoxamine and other sigma-1 receptor agonists to improve cognitive dysfunction and promote neuronal recovery processes in a broad range of psychiatric illnesses, including MDD, anxiety disorders, Alzheimer's disease and schizophrenia.

This is a review and summary of Professor Hashimoto's presentation at an Abbot-sponsored Symposium held in Hong Kong, 2010.

References: see page 8

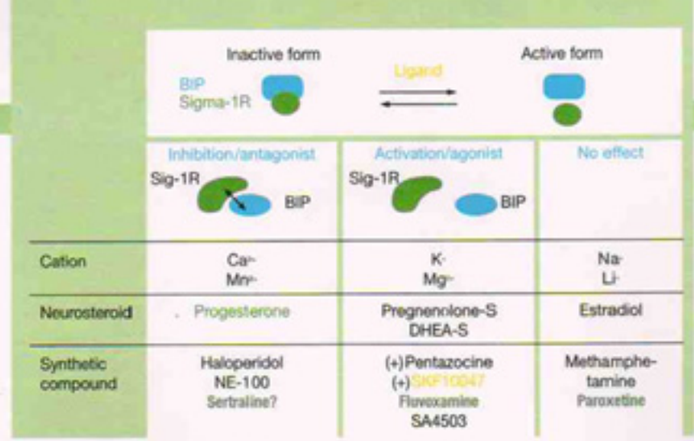


Figure 2. Receptor chaperone - a novel concept in pharmacology

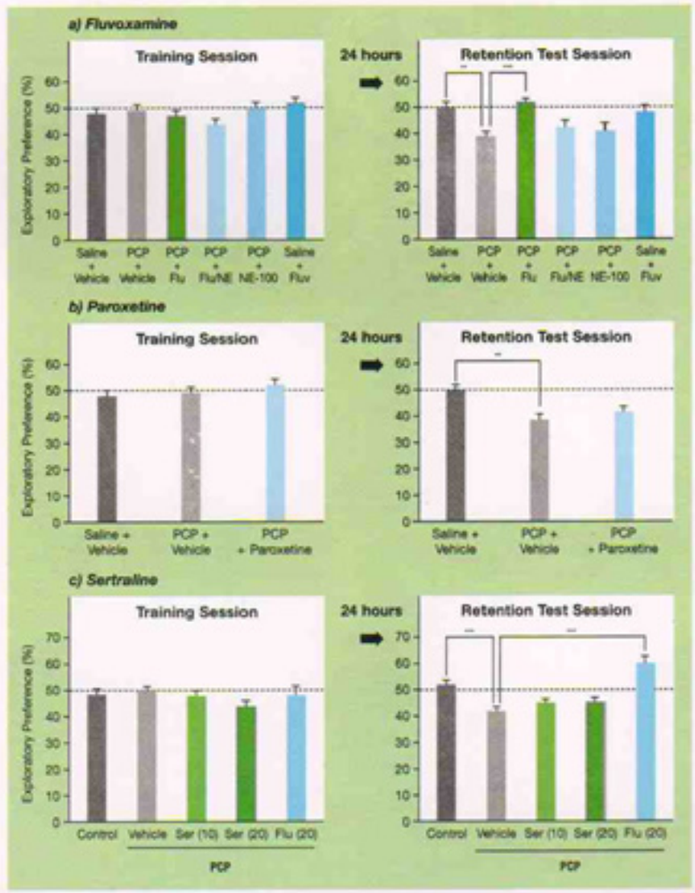


Figure 3. Improvement in PCP-induced cognitive defects by fluvoxamine (a)5 but not by paroxetine (b)5 or sertraline (c)[6]

Figure 4. I[11C]SA4503-PET images in healthy human brain