ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2012 June 22; 2(3): 43-57

Baishideng Publishing Group
www.wjgnet.com

WJP World Journal of Psychiatry

A peer-reviewed, online, open-access journal of psychiatry

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2011-2015

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WJP World Journal of Psychiatry

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Bimonthly Volume 2 Number 3 June 22, 2012

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World Journal of Psychiatry
Volume 2 Number 3 June 22, 2012

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Bimonthly

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Telephone: +852-58042046
E-mail: bpg@baishideng.com
http://www.wjgnet.com

PUBLICATION DATE
June 22, 2012

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3206/g_info_20100722180909.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Psychiatry

Online Submissions: http://www.wjgnet.com/esps/
wjp@wjgnet.com
doi:10.5498/wjp.v2.i3.43

World J Psychiatr 2012 June 22; 2(3): 43-48
ISSN 2220-3206 (online)

REVIEW

Positive aspects of caregiving in schizophrenia: A review

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Received: November 15, 2011 Revised: June 19, 2012
Accepted: June 20, 2012
Published online: June 22, 2012

Abstract

Schizophrenia is a severe mental illness which is associated with significant consequences for both the patients and their relatives. Due to chronicity of the illness, the relatives of patients of schizophrenia have to bear the main brunt of the illness. Studies across the world have evaluated various aspects of caregiving and caregivers such as burden, coping, quality of life, social support, expressed emotions, and psychological morbidity. In general the research has looked at caregiving as a negative phenomenon, however, now it is increasingly recognised that caregiving is not only associated with negative consequences only, also experience subjective gains and satisfaction. This review focus on the conceptual issues, instruments available to assess the positive aspects of caregiving and the various correlates of positive aspects of caregiving reported in relation to schizophrenia. The positive aspect of caregiving has been variously measured as positive caregiving experience, caregiving satisfaction, caregiving gains and finding meaning through caregiving scale and positive aspects of caregiving experience. Studies suggests that caregivers of patients with schizophrenia and psychotic disorders experience caregiving gains (in the form of becoming more sensitive to persons with disabilities, clarity about their priorities in life and a greater sense of inner strength), experience good aspects of relationship with the patient, do have personal positive experiences. Some of the studies suggest that those who experience greater negative caregiving experience also do experience positive caregiving experience.

Key words: Schizophrenia; Caregiving; Positive aspects

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Kulhara P, Kate N, Grover S, Nehra R. Positive aspects of caregiving in schizophrenia: A review. *World J Psychiatr* 2012; 2(3): 43-48 Available from: URL: http://www.wjgnet.com/2220-3206/full/v2/i3/43.htm DOI: http://dx.doi.org/10.5498/wjp.v2.i3.43

INTRODUCTION

Early onset of the illness, persistence of symptoms in the long run and chronic relapsing course of schizophrenia has far-reaching consequences for both the patients with schizophrenia and their relatives. Due to the illness, the patients may have diminished capacity for social relationships, they may not be able to take care of themselves and their day-to-day needs, face reduced employment opportunities and if employed, may be less productive. The illness thus hampers independent living and may lessen life satisfaction. Family members of patients with schizophrenia are often confronted with uncertainty about the

course of the illness, lack of reciprocity in relationship with the patient and the trepidation of unpredictable symptoms. They also have to meet the cost of care (direct, indirect and intangible) besides accepting patient's lost potential and impending unemployment or reduced prospects of employability of the patient. No wonder the caring relatives often experience grief and have to cope with stigma and social isolation, which leaves them with a feeling of shame, embarrassment or guilt. Thus, the illness leads to considerable emotional, financial and real-world demands on those close to the sufferer, typically the parents or the spouse. Moreover, studies have shown that caregiving frequently leads to mental morbidity, neglect of health of self and higher risk of mortality[1-4]. Caregivers also experience gradual burnout while caring for their loved ones[5]. Parents, spouses, and siblings are often unable to deal with their own individual or family developmental needs because the focus is so often on the care of the relative with schizophrenia[6]. Many studies across the world have evaluated various aspects of caregiving and caregivers such as burden, coping, quality of life, social support, expressed emotions, psychological morbidity *etc*. Till recently, caregiving was thought to be a negative phenomenon, however, now it is increasingly recognised that caregiving is not only associated with negative consequences only, but the caregivers also experience subjective gains and satisfaction. In this article we focus on the conceptual issues and current understanding of positive aspects of caregiving and review research regarding these in relation to schizophrenia.

CONCEPT OF POSITIVE ASPECTS OF CAREGIVING

Positive caregiving experience is a subjective event, as such no standard formal definition of this is available. Various authors have understood positive caregiving in terms of caregiver gains, satisfaction and caregiving experience[7-9]. Many researchers have assessed positive caregiving experience in the domains of duty/obligation, companionship, fulfillment, reward, quality of life, enjoyment, meaning, *etc*.[10], caregiver esteem[11,12], uplifts of caregiving[13,14], finding or making meaning through caregiving[15-18] and caregiver appraisal[19,20]. Hunt[21] has extensively reviewed negative and positive aspects of caregiving. Next we will briefly discuss the positive aspects of caregiving.

Kramer[22] gave the concept of caregiver gain after a critical review of literature on positive aspects of caregiving, and described it as "the extent to which the caregiving role is appraised to enhance an individual's life space and be enriching". It may include any positive yield to the caregiver as a result of the caregiving experience. Kramer[22] proposed a model of caregiver adaptation in which "appraisal of role gain" is an intervening process through which background and contextual variables act to influence well being. It is suggested that caregiving gains may be related to the resources like coping and social support that the caregiver possesses. Kramer[22] also tried to conceptualize gain as both an event-specific and a role related construct. Event-specific gain includes responses to specific caregiving tasks, and role-specific gain pertains to more general appraisals of the caregiving role. Other authors have defined caregiver gains as "the caregiver's perceived personal growth and enhanced interpersonal relationships"[23].

The caregiving benefits/gains described in the literature include feeling more useful, feeling needed, learning new skills, and adding meaning to one's sense of self[24,25], gaining a sense of fulfillment for meeting a duty/obligation and enjoyment derived from caregiving itself or from companionship with the care recipient[10].

Caregiver satisfaction is one of the most commonly used terms with respect to positive aspects of caregiving[22]. Initially caregiver satisfaction was defined as "the benefits occurring to the caregiver through his or her own efforts"[20]. Later, the same group of authors defined caregiver satisfactions as, "subjectively perceived gains from desirable aspects of or positive affective returns from caregiving"[19] or "the result of caregiving experiences that give life a positive flavor"[25]. It has been shown that caregiver satisfaction may be related to positive affect and to burden[20,25]. Tarlow *et al*[26] considered positive aspects of caregiving as the reward and satisfaction derived from the caregiving relationship. Other studies have identified satisfaction with caregiving in the form of feeling fulfilled, important, and responsible, to finding a sense of companionship and meaning within the relationship[10].

Nolan *et al*[8], described 3 dimensions of "caregiving satisfaction"-satisfaction derived mainly from the interpersonal dynamics between carer and the cared for person, satisfaction derived from intrapersonal or intrapsychic orientation of the carer and satisfactions derived mainly from a desire to promote a positive or avoid a negative outcome for the care recipient.

Another positive aspect of caregiving cited in the literature includes "Uplift". Kinney *et al*[27] defined uplift as an event that makes one feel good, makes one joyful, or makes one glad or satisfied. Uplifts are also understood as "daily events that evoke feelings of joy, gladness, or satisfaction"[13]. It is hypothesized that uplifts buffer the effects of hassles[27]. Studies have shown that when uplifts outweighed hassles, caregivers reported less distress[13].

The construct "finding meaning through caregiving" is another aspect of positive caregiving and was initially identified in a preliminary qualitative study of family caregivers of persons with dementia in which the caregivers responded to a series of open-ended questions, and the researchers identified 6 major themes based on the qualitative analyses of the responses[28]. Later, the authors developed a 135-item "Finding Meaning Through Caregiving Scale (FMTCS)" and tested its psychometric properties[17]. They identified 3 subscales: Loss/Powerlessness, which identifies difficult aspects of caregiving; Provisional Meaning, which identifies how caregivers find day-

to-day meaning; and Ultimate Meaning, which identifies philosophical/religious/spiritual attributions associated with the experience of caregiving.

Caregiver esteem is another facet of positive caregiving which has caught the attention of researchers and is assumed to be the extent to which performing caregiving tasks enhance the caregiver's self-esteem.

Some studies have also demarcated positive aspects of caregiving as improved relationships, feeling appreciated, pleasure, and prevention of further deterioration[22,29]. Other positive aspects which have been studied include positive caregiving experience which has two components, positive personal outcomes and good aspects of the relationship with the patient[7].

MEASURING POSITIVE ASPECTS OF CAREGIVING

The positive caregiving experience, as measured by Experience of Caregiving Inventory (ECI) of Szmukler *et al*[7] is based on the concept of caregiving appraisal, which involves both positive and negative facets of the caregiving experience. The ECI has eight subscales measuring the negative experiences while two subscales quantify the positive caregiving experience-positive personal outcomes and good aspects of the relationship with the patient. Studies based on ECI have shown positive correlation between positive and negative caregiving experience. However, this scale does not ascertain many other positive aspects of caregiving. Caregiver appraisal scale was designed to measure caregiver satisfaction and it chiefly assesses caregiver satisfaction in relation to caring for elderly family members. It includes a subscale on caregiver satisfaction, wherein caregiver satisfaction is measured by questions such as-"patient's pleasure over something gives you pleasure, you are happy knowing that patients is being cared for by the family, helping patient makes you feel closer to him/her, the patient shows appreciation for what you do for him/her", *etc*. Other components of caregiving assessed by Caregiver appraisal scale are caregiver ideology and caregiving mastery[30].

Pearlin[31] designed a 10 item Caregiving Gains Scale to assess caregiving gain which was later adapted by researchers and has been used to study caregiving gains in caregivers of mentally ill subjects[24,30,32]. "FMTCS" was developed by Farran *et al*[28], which is a 7-point Likert-type 43 item questionnaire. Psychometric evaluation of scale identified 3 subscales: Loss/Powerlessness identifying difficult aspects of caregiving; Provisional Meaning, which identifies how caregivers find day-to-day meaning; and Ultimate Meaning, which labels philosophical/religious/spiritual attributions associated with the experience of caregiving. Of these various scales, ECI has commonly been used to study the positive aspects of caregiving in relation to schizophrenia.

We recently developed a Scale for Positive Aspects of Caregiving Experience (SPACE). For developing this scale, available scales (ECI[7], Caregiver Appraisal Scale[8], Adapted Caregiver Gains scale[23], Positive Aspects of Caregiving[27]) assessing some aspect of positive caregiving were reviewed. Items were taken from these scales and common items were condensed and accordingly incorporated in SPACE. Then the scale was evaluated in the caregivers of patients with schizophrenia and was found to have good internal consistency, test- retest reliability, cross language reliability, split half reliability and face validity. Principle Component Analysis yielded a factor structure comprising four factors. The factor so obtained also had good test- retest reliability. The 4 factor domains of positive caregiving identified are caregiving personal gains, motivation for caregiving role, caregiver satisfaction and self-esteem and social aspect of caring[33].

POSITIVE ASPECTS OF CAREGIVING IN APPRAISAL PARADIGM

Caregiver appraisal is a neutral term in that it can indicate positive, neutral, or negative feelings about the caregiving situation. It is based on the transactional perspective wherein it is understood as a transaction between the person and the environment[34]. To "appraise" is understood as to "set a value on", "estimate the amount of", or "evaluate the worth, significance, or status of" something[22]. Therefore, caregiver appraisal refers to the process by which a caregiver estimates the amount or significance of caregiving, in which he takes into consideration both the nature of the stressor and his or her resources to cope with these. Hence, caregiving appraisal may be positive, negative, or neutral[35] and consists of subjective cognitive and affective appraisals of the potential stressor and the efficacy of one's coping efforts[19]. So "appraisal of caregiving" is understood as a construct existing in the "stress-appraisal-coping" framework, and suggests that the experience of caregiving results from an interaction between the relative's illness and factors in the carer' s external and internal world. According to this, patient's illness, associated behaviors, disabilities and the perceived disruptions of the carers' life are appraised as stressors by the carers. The carer's personality, quality of family relationships and degree of social support are considered as the mediating factors in caregiver's appraisal of the stress[7,23,36]. A caregiver may appraise the whole caregiving experience as positive, negative or both depending on the interaction between the various variables and the outcome is understood in the form of psychological morbidity. However, it is possible that not all caregivers will experience psychological morbidity; hence, it would be prudent to consider other outcome measures like quality of life.

Thus, while evaluating the positive aspects of caregiving, it would be worthwhile to evaluate the caregivers coping ability, social support, psychological morbidity, quality of life, perceived burden and level of caregiving involvement and caregiving consequences.

POSITIVE ASPECTS OF CAREGIVING IN PSYCHOTIC DISORDERS

Few studies have evaluated positive aspects of caregiving in patients with schizophrenia, schizophrenia spectrum disorders and patients with psychosis. Chen and Greenberg[23] assessed 560 caregivers of patients with schizophrenia spectrum disorders through telephonic interview on Caregiving Gains Scale developed by Pearlin[31]. They found that although the experiences of gains were quite prevalent, not all respondents had positive experiences with all aspects of gains. Almost 70% of the caregivers reported that they had become more sensitive to persons with disabilities. More than 50% reported that caring for their relative helped them significantly in clarifying their priorities in life and generated a greater sense of inner strength. Tarricone *et al*[37] compared the experience of caregiving in patients with psychosis in 95 Italian patients and their caregivers with 69 British patients and caregivers on the ECI. They found no significant difference with regards to the positive caregiver appraisal between the two samples. However, they found that the caregivers in both the samples valued the "good aspects of relationship" more than "the personal positive experiences" in the positive domains of the caregiving. Addington *et al*[38] followed up 185 caregivers of patients with 1st episode psychosis and evaluated them on the ECI at baseline and each year of follow-up, with 91 caregivers continuing in the study after the 3 year period. They found that these caregivers prized the positive personal experiences more than the good aspects of the relationship during each assessment of the caregiver during the study period. Treasure *et al*[39] compared 68 caregivers of patients diagnosed to have psychosis with 71 caregivers of patients with anorexia nervosa and found that the caregivers of patients with psychosis valued the positive personal experiences more than the good aspects of the relationship with their patient while the opposite was true for the caregivers of anorexia nervosa. In addition, caregivers of patients with psychosis experienced a lower total positive score on ECI. Aggarwal *at al*[40] evaluated 50 caregivers of patients with schizophrenia using the ECI. They found that caregivers valued the domain of good aspects of relationship more than the personal positive experiences domain. We compared caregiving experience of caregivers of patients with schizophrenia with caregiving experience of caregivers of patients with bipolar disorder using ECI and found that caregivers of patients with schizophrenia had overall more positive and negative appraisal of caregiving experience while caring for their ill relatives. However, there was a significant positive correlation between the negative and positive caregiving experience score for both schizophrenia and bipolar groups[41].

RELATIONSHIP BETWEEN POSITIVE ASPECTS OF CAREGIVING AND BURDEN

Relationship between positive and negative aspects of caregiving has been studied using ECI or use of burden scale and scales assessing some positive aspect of caregiving. Hsiao *et al*[42] reported that family caregivers with a more positive interpretation of family caregiving reported lower levels of family caregiver burden. In another study, Pickett *et al*[29] reported that parent's positive appraisals of their relationships with their mentally ill adult child were significantly related to decreased levels of caregiver burden. Studies which have assessed caregiving experience using ECI suggests that caregivers who appraise the caregiving experience more negatively also appraised the same more positively[38,40,43,44]. However, some of the studies have not reported any relationship between positive and negative caregiving experience as assessed by ECI[45].

CORRELATES OF POSITIVE ASPECTS OF CAREGIVING IN PSYCHOTIC DISORDERS

While the positive aspects of caregiving have been recognized, the importance of recognizing factors associated with positive aspects of caregiving is being increasingly acknowledged. Current research has begun to focus on the correlates of positive aspects of caregiving. Although research in this sphere is still in a nascent stage, some studies have shown that positive aspects of caregiving are influenced by socio-demographic, clinical and psychological variables.

Studies show more educated caregivers report higher levels of positive personal experiences, higher level of perception of good aspects of relationship[40,44] and overall positive caregiving experience[24,44]. More positive caregiving experiences are noted when the patients are females[30,46], when the caregivers are men of an older age group and when caregivers have low family incomes[47]. Some studies have also shown that caregivers of patients who were young[42] and unemployed[24,43,44] reported less positive experiences. However other investigations do not show significant relationship between the caregiving appraisals and age, gender and employment of the caregiver[29].

The relationship between caregiving and the psychopathology is rather inconsistent. One study reported that the caregivers of patients with higher positive symptoms of schizophrenia reported more positive caregiving experience[46]. Another study showed that higher scores on "avolition-apathy" domain of negative symptoms as measured by the Scale for Assessment of Negative Symptoms was associated with lower positive appraisals[24]. Some studies do not show significant relationship between relatives' appraisal of caregiving and patients' symptomatology[43,48]. Better patient functioning is related to greater positive appraisal of caregiving according to some investigators[23,43,48]. One study reported higher positive caregiving experience when there was a family history of psychosis[43]. Onwumere *et al*[49] reported that positive caregiving appraisals were more common in caregivers of patients with longer illness duration.

With regards to the level of involvement of caregiver in the patients care, it has been shown that caregivers

report more positive experience when the caregiver had shared a better previous and current relationship with the care recipient, had fewer daily hours of responsibility as a caregiver, and when they had become caregivers by their own initiatives[47]. A study assessing the caregiver's gains among older parents of adults with serious mental illness reported that parents who provided more help to their children with mental illness reported more gains than parents who were less involved in helping their children. This study also found that the amount of help the parent provided correlated significantly with the amount of assistance the child provided to the parent, suggesting reciprocity in the relationship[50].

Many psychological variables like coping strategies, religious practices and perceived social support have been shown to have some influence on the positive caregiving experience. Studies involving coping skills show that the caregivers who use problem focused coping strategies and seek social support as a coping strategy experience a higher level of positive personal caregiving experiences[44]. A study from India, found that less use of denial and greater use of problem solving coping was associated with greater caregiver well being[51]. There is no consensus with regard to use of religious coping strategies with some studies showing that religious coping strategies frame the caregiving experience in a positive manner[51], while other studies report that religious coping had little influence on the caregiver well being outcomes[52]. There are very few studies that have evaluated the relationship of religious practices with positive aspects of caregiving. One study reported that religiosity was associated with better self-esteem and self-care and less of depression among the family caregivers[53]. Social support also plays an important role in positive aspects of caregiving as significant positive associations between the experience of caregiving benefits/gains and family socio-emotional support[40] have been reported. Onwumere *et al*[49] studied caregivers of patients with nonaffective psychosis and reported that positive caregiving appraisal correlated with higher levels of perceived caregiver and patient control of the illness. Predominately illness beliefs were significant predictors of caregiving appraisal and distress rather than illness length, caregiver ethnicity, or type of caregiver. Aschbrenner *et al*[50] assessed the caregivers gains among older parents of adults with serious mental illness and reported that support from an adult child with serious mental illness, presence of more number of confidants and being member of the parent's support group were the variables which were positively and significantly correlated with personal gains for the parent. Another study which evaluated reciprocal exchange between a mentally ill and other family members, reported that amount of support patients give to their parents and siblings is strongly associated with how much support they receive from family members[54].

CONCLUSION

In current schizophrenia literature, research involving burden experienced by caregivers grossly overshadows studies regarding positive aspects of caregiving. However, this scenario is changing and positive aspects of caregiving are drawing more investigative attention. Studies from various cultures have shown that perception of family burden varies across different contexts and that these variations are only partially explained by patients, carers and relationship features and hence it would be inappropriate to compare or generalize the findings of studies from one culture to another. Similarly, it is expected that the positive aspects of caregiving will also be influenced by the cultural factors. Studying positive aspects of caregiving will help the clinicians in identifying and promoting factors that contribute to positive caregiving, improve the mental health of the caregiver and thereby enhance the overall care of their patients in a particular cultural setting.

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S- Editor Lu YJ **L- Editor** A **E- Editor** Zheng XM

World Journal of Psychiatry

Online Submissions: http://www.wjgnet.com/esps/
wjp@wjgnet.com
doi:10.5498/wjp.v2.i3.49

World J Psychiatr 2012 June 22; 2(3): 49-57
ISSN 2220-3206 (online)

REVIEW

Neuroplasticity and major depression, the role of modern antidepressant drugs

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Received: November 3, 2011 Revised: June 19, 2012
Accepted: June 20, 2012
Published online: June 22, 2012

Abstract

The pathophysiology of depression has been traditionally attributed to a chemical imbalance and critical interactions between genetic and environmental risk factors, and antidepressant drugs suggested to act predominantly amplifying monoaminergic neurotransmission. This conceptualization may be currently considered reductive. The current literature about the pathophysiological mechanisms underlying depression, stress-related disorders and antidepressant treatment was examined. In order to provide a critical overview about neuroplasticity, depression and antidepressant drugs, a detailed Pubmed/Medline, Scopus, PsycLit, and PsycInfo search to identify all papers and book chapters during the period between 1980 and 2011 was performed. Pathological stress and depression determine relevant brain changes such as loss of dendritic spines and synapses, dendritic atrophy as well as reduction of glial cells (both in number and size) in specific areas such as the hippocampus and prefrontal cortex. An increased dendritic arborisation and synaptogenesis may instead be observed in the amygdala as a consequence of depression and stress-related disorders. While hippocampal and prefrontal functioning was impaired, amygdala functioning was abnormally amplified. Most of molecular abnormalities and biological changes of aberrant neuroplasticity may be explained by the action of glutamate. Antidepressant treatment is associated with neurogenesis, gliogenesis, dendritic arborisation, new synapse formation and cell survival both in the hippocampus and prefrontal cortex. Antidepressants (ADs) induce neuroplasticity mechanisms reversing the pathological effects of depression and stress-related disorders. The neuroplasticity hypothesis may explain the therapeutic and prophylactic action of ADs representing a new innovative approach to the pathophysiology of depression and stress-related disorders.

Key words: Neuroplasticity; Neurogenesis; Depression; Stress-related changes; Antidepressants

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Serafini G. Neuroplasticity and major depression, the role of modern antidepressant drugs. *World J Psychiatr* 2012; 2(3): 49-57 Available from: URL: http://www.wjgnet.com/2220-3206/full/v2/i3/49.htm DOI: http://dx.doi.org/10.5498/wjp.v2.i3.49

INTRODUCTION

Major depressive disorder (MDD) is a common and invalidating mental illness affecting approximately 2.5% of the general population. MDD is one of the leading cause of disability and it has been suggested to become the second highest burden of disease (measured in disability-adjusted life years) by 2020[1]. MDD has negative social consequences in terms of reduced employment and psychosocial impairment[2]. The pathophysiology of depression involves both external social stressors and internal genetic vulnerability.

Among all biological theories postulated about MDD, an impairment of neuroplasticity and cellular resilience has been suggested[3]. According to this theory, neural circuits and connections undergo lifelong modifications and reorganizations in response to external or internal environmental stimuli. Adult neurogenesis involves precursors of cell proliferation, migration and differentiation mainly occurring in the dentate gyrus of the hippocampus[4]. Several neurotoxic agents such as chronic stress, excessive concentrations of glutamate, biogenic amines and glucocorticoids may affect the morphology of some neural cells such as hippocampal CA3 pyramidal neurons and pyramidal cells of prefrontal cortex. Neural cells may react to chronic stress debranching apical dendrites or with spine loss and these changes are closely associated to daily periods of resting and activity[5,6]. Interestingly, some antidepressants (ADs) may increase neurotrophin signalling promoting neuronal and synaptic remodelling as well as the formation of new neurons in the hippocampus and prefrontal cortex[3,7-11]. Modern ADs may act enhancing neuroplasticity mechanisms and renewing the impairment in neural circuits contributing to their normalization[3,12,13]. Although precise modifications induced at the synaptic level by ADs are still unclear, it's well known that ADs may promote neuronal connectivity and strengthen specific synapses or normalize glutamatergic tone which is supposed to be underlying major depression[14]. Pharmacological manipulation of the glutamatergic system in animal models has been shown to reduce stress-induced morphological changes in the hippocampus[11,15,16] and some ADs have been reported to regulate glutamatergic transmission through the inhibition of stress-induced morphological changes in both the hippocampus and amygdala[11].

LITERATURE REVIEW

In order to provide a critical overview about neuroplasticity, depression and ADs, a detailed Pubmed/Medline, Scopus, PsycLit, and PsycInfo search to identify all papers and book chapters during the period between 1980 and 2011 was performed. The search used the following terms: "Major Depression Episode" AND "Affective Disorders" AND "Neuroplasticity" OR "Neurogenesis" OR "Synaptic plasticity" AND "ADs" OR "Antidepressant drugs" OR "Antidepressant medications" OR "Antidepressant agents" AND "Treatment" OR "Intervention" OR "Future implications". Reference lists of the articles were also manually checked for relevant studies. Included papers were restricted to those in English. Only those articles published in peer-reviewed journals were included. Where a title or abstract seemed to describe a study eligible for inclusion, the full article was obtained and examined to assess its relevance based on the inclusion criteria. Approximately 80 full-text articles met our inclusion criteria and were reviewed. Two independent researchers conducted a two-step literature search. Any discrepancies between the two reviewers who, blind to each other, examined the studies for the possible inclusion were resolved by consultations with a senior author.

NEUROPLASTICITY AND MAJOR DEPRESSION

Generally, resiliency is the ability to adapt and react to stressful life events and environmental situations. This ability is mediated by the involvement of several brain areas such as the hippocampus, amygdala, and prefrontal cortex playing a key role in either cognitive and affective domains and requiring the involvement of specific neurotransmitter molecules. Neuroplasticity is instead a general term indicating a neural framework in which all the different internal events at either the molecular and systemic levels produce neuronal modifications[14]. In the last decades, the view that the brain is a static structure in which electrical and chemical information are processed within a fixed system has been widely debated. Neural circuits, brain nuclei, neurons and synaptic connections undergo several lifelong modifications and relevant adaptations due to environmental stimuli through the neural plasticity mechanisms. Continuous modifications such as increased axonal growth and collateral sprouting determine the development of new synapses and a retrograde elimination of the pre-existing synapses as well as changes in the dendritic tree and spine density influencing the number of post-synaptic sites[17,18]. Popov and Bochorova[19] found that specific and multifaceted structural changes at synapse level may be induced by mossy fibres and hippocampal pyramidal neurons. Also, hippocampal CA3 pyramidal neurons undergo dendritic shrinkage after chronic stress induced by corticosterone[20-22].

Neurohistological changes associated with pathological stress and antidepressant response are site-specific[23]. Reduced hippocampal volume is one of the most common finding in depressed subjects and longer duration of depressive episodes is known to be closely related to modifications in hippocampal volume[24,25]. It has been suggested that somatodendritic, axonal, synaptic and glial cell number changes are all involved in the inhibition of adult hippocampal neurogenesis. The reduction of hippocampal volume may be observed in post-mortem animal models of either stress and major depression[13,26]. In animal models, stress-induced hippocampal neuropathological changes may be summarized as follows: loss of dendritic spines; decrease in the number and length of dendrites; loss of synapses; loss of glia and impairment of neurogenesis[13,26-30]. The retraction of dendrites and synapses determine a reduction of connectivity, multiple impairments of neurons associated with loss of glia, consequent reduction of neurotransmission, decreased neurogenesis[23]. Recent evidence[31] suggested that both hypercholesterolemia (no post-mortem neuronal loss was found in the brain tissue) and apoptosis (evident only in a small hippocampal area) have not been identified as possible neurotoxic agents. Additionally, Reif *et al*[32] did not find in a small sample of subjects evidence of reduced neural stem cell proliferation possibly explaining the changes in neurogenesis of depressed patients.

Stress-induced neurohistological changes do not sim-

ply interfere with hippocampal functioning but they also affect functioning of other downstream areas. Several structural changes have been shown in the rat prefrontal cortex, a brain area in which a retraction of dendrites and spine loss induced by chronic stress and associated with daily periods resting and activities have been described[5,6]. Post-mortem histopathological studies[33,34] have shown reduced neuronal density, smaller neuronal somata and a relevant reduction in prefrontal cortical thickness. A stress-induced inhibition of cell proliferation and gliogenesis, specifically, a stress-induced dendritic reorganization in pyramidal neurons of the medial prefrontal cortex has been commonly observed. In animal models, stress-induced neurohistological changes in the prefrontal cortex determine loss of dendritic spines, atrophy of the dendritic tree, loss of synapses, decreased number and size of glia[13,26,28,30]. Post-mortem studies in depressed subjects have shown a decrease in neuronal and glial cells (both in number and size), and overall cortical thickness[26]. A glial cells loss was also found in limbic and extralimbic structures, prefrontal, orbitofrontal and cingulated cortices of depressed individuals.

Moreover, structural modifications have been described in the amygdala where an enhanced dendritic arborisation (but not an increase in all classes of amgdaloid neurons) has been shown by Vyas *et al*[35]. After chronic stress they observed an enhanced dendritic arborisation in the basolateral nucleus of the amygdala and specifically in the pyramidal and excitatory projections of the stellate neurons. Also in animal models, stress-induced neurohistological changes in the amygdala include increased dendritic arborisation and synaptogenesis[13,30]. No alteration was reported in neuronal amygdalar number although a reduced number of glial cells has been demonstrated in depressed patients[36]. Several studies[37,38] using MRI analysis showed an altered amygdalar core. Overall, an increased amygdalar volume determining not only structural but also functional impairments has been described in either stressed animals and depressed subjects. Stress-induced neurohistological modifications in the amygdala were not reversed after some weeks but required longer periods[13].

In addition, chronic stress changes on dendrites and spines influence the expression of several synaptic molecules resulting crucial for the information transfer between neurons. Cooper *et al*[39] showed that the expression of M6a, particularly the splice variant M6a-Ib, a glycoprotein which appears located in the axonal plasma membrane of glutamatergic neurons may be differently regulated by stress. Chronic stress may differently induce the expression of M6a-Ib in a region-dependent manner down-regulating M6a-Ib in the dentate gyrus granule neurons and CA3 pyramidal neurons and an up-regulating M6a-Ib in the medial prefrontal cortex. This different regulation of targeted glycoproteins induced by chronic stress presumably leads to reduced axonal output in hippocampal neurons also altering the integrity of axons and the information transfer between neurons in different brain regions. Chronic stress may also affect neuron-glia communication inducing a remodelling of hippocampal dendrites and an increased expression of GLT-1 glial glutamate transporter in the dendate gyrus and CA3 hippocampal neurons[16].

Therefore, both pathological stress and major depression result in abnormalities in neuroplasticity response characterized by altered increased activity in the amygdala and impaired hippocampal and prefrontal cortex functioning[40]. The hippocampus is a key structure involved in learning and memory, the prefrontal cortex plays a key role in cognitive functions such as attention, concentration, learning and memory whereas the amygdala plays a fundamental role in social and emotional learning and, particularly, in emotions such as anxiety and fear.

NEUROPLASTICITY AND MODERN ANTIDEPRESSANT DRUGS

Several lines of evidence demonstrate that some modern ADs may reverse neuroplasticity and neurogenesis modifications induced by chronic stress[13]. In animal models, ADs may reverse and remodel many of the stress-induced neurohistological changes. It is possible to speculate that by reversing the neurohistological effects of stress in animal models, ADs may attenuate depression in human subjects. There is evidence that treatment with modern ADs significantly improves both hippocampal shrinkage[28,41] and functions (e.g., cognitive functions)[42]. Interestingly, Rocher *et al*[43] suggested that both tianeptine and fluoxetine may reverse the inhibition of long-term potentiation (an interesting prototype of synaptic plasticity) not only in the hippocampus but also in prefrontal cortex. Czeh *et al*[44] suggested that tianeptine may inhibit the stress-induced reduced number of hippocampal astrocytes reversing morphological modifications observed in the somal volume.

The exact mechanism underlying neuroplasticity dysfunctions is still unclear[45,46]. Evidence suggest a central role of both N-Methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors activation in inducing morphological changes regulating neuroplasticity such as dendritic length and branching, spine density and volumes of several brain regions, specifically in the hippocampal dentate gyrus[47,48]. Glutamate, in certain concentrations and presumably under the influence of elevated glucocorticoids levels, mediates a structural remodelling of neurons leading to reversible modifications such as reduced neurogenesis, neuronal shrinkage and decreased growth[49]. Several authors[50,51] showed that the inhibition of glutamate release by NMDA receptors prevents this remodelling. Of particular interest is also the evidence suggesting that suicidal ideation in depressed subjects is associated with genes encoding ionotropic glutamate receptors[52].

Some ADs and electroconvulsive shock therapy may reverse reduced neurogenesis, neuronal shrinkage and decreased growth, modifying glutamate impairment in the an-

terior cingulated of depressed individuals[53]. Drugs having mood stabilization properties with additionally modulating glutamate release may mediate morphological plasticity abnormalities[11] and stress-induced morphological hippocampal/amygdalar changes which are reduced by antidepressant manipulation[11,16]. Specifically, Malberg *et al*[54] found that tianeptine prevented the retraction of apical dendrites of hippocampal CA3 pyramidal neurons and the increased granule cell proliferation. While tianeptine may prevent glutamate efflux in the basolateral nucleus of the amygdala, this effect seem not to be induced with the administration of fluoxetine. Reznikov *et al*[55] postulated that the impact of ADs in mediating the stress-induced neuropathological changes was quite specific. Interestingly, Emery *et al*[56] found that neural stem cells involved in the proliferation and differentiation of adult new neurons extended axons to the CA3 region 2 wk after antidepressant administration explaining at least partially the delayed clinical improvement induced by ADs.

However, what are the molecular mechanisms underlying antidepressant regulation of neuroplasticity and neurogenesis? Svenningsson *et al*[57] suggested that ADs may induce a phosphorilation of AMPA receptors in two main sites of the subunit GluR1: Ser831 which is phosphorilated by protein chinase C or CaMK-Ⅱ determining elevations in hippocampal currents[58] and Ser845 which appears crucial for protein chinase A amplification of peak current by GluR1 receptors[59]. Imipramine and fluoxetine act increasing the phosphorilation at Ser845 on the subunit GluR1[60,61], while tianeptine may reverse stress-induced changes in glutamate receptors expression[16], impairment of neurogenesis[44] and reduced stress-induced apoptosis in the hippocampus and temporal cortex[62]. Also, other mechanisms of action have been hypothesized. ADs of different classes act enhancing phosphorilation at the c-AMP regulatory element-binding protein (CREB)[63] and CaMK-Ⅱ[64] as well as electroconvulsive shock therapy has been demonstrated to increase hippocampal CREB phosphorilation[65]. Specific neurotrophic factors such as brain-derived neurotrophic factor (BDNF) binding to tyrosine kinase (TrK) receptors may activate intracellular cascades involving cAMP-dependent protein kinase A (PKA), mitogen-activated protein kinase (MAPK), CaMK-Ⅱ and also transcription factors such as CREB. CREB is involved in the synthesis of different enzymes and proteins considered crucial in inducing structural changes underlying neuroplasticity. CREB and BDNF are some of the most important effectors of neuroplasticity[13,26]. Additionally, ADs may increase the activity of c-fos, a marker of biochemical activity[66]; some ADs such as tianeptine may reduce c-fos levels reversing its previous stress-induced increase[67]. Tianeptine has been demonstrated to prevent impaired stress-induced amygdalar and prefrontal changes[50,68] also preventing the reduction of length and branching of apical dendrites of the hippocampal CA3 neurons exposed to stress[21,50]. Rocher *et al*[43] suggested that fluoxetine possesses a similar slower activity blocking the effect of stress in the prefrontal cortex. The final result of all these intracellular signalling cascades is a stimulation of neurogenesis in the dentate gyrus including an increase of glial cells in the complexity of dendritic branching as well as the formation of new synaptic connections[69].

Also, agomelatine has been proposed to promote hippocampal neurogenesis under basal conditions[70,71]. Agomelatine has been found to selectively increase cell proliferation and neurogenesis in the ventral hippocampus and to enhance the survival of newly generated cells throughout the entire hippocampus in rats under either basal and stressful conditions[72,73]. Other evidence[74-76] suggested that agomelatine may stimulate adult neurogenesis in the hippocampal dentate gyrus reducing the increase of glutamate release induced by acute stress in the prefrontal and frontal cortex[77].

Recently, Morley-Fletcher *et al*[78] found that both a 3- or 6-wk treatment with agomelatine (40-50 mg/kg daily) may reverse the reduced hippocampal levels of phosphorylated CREB in adult prenatal restraint stress rats as well as the reduced hippocampal levels of mGlu2/3 and mGlu5 metabotropic glutamate receptors together with the reduced neurogenesis in the ventral hippocampus (this structucture is specifically involved in encoding memories associated with stress and emotions). In addition, Dagyte *et al*[79] found that treatment with agomelatine normalized stress-affected neuronal activity and promoted neurogenesis in the hippocampus of rats exposed to chronic footshock stress. They suggested that chronic stress reduced c-Fos expression in the hippocampal dentate gyrus and that chronic agomelatine treatment reversed this effect normalizing neuronal activity to basal levels with enhanced hippocampal cell proliferation and survival in chronically stressed rats. They also reported that chronic mild stress significantly decreased the newborn cell survival and doublecortin expression in the dentate gyrus but these changes can be reversed with agomelatine that completely normalized stress affected cell survival and partly reduced double cortin expression. AlAhmed and Herbert[74] found that agomelatine through an intact diurnal corticosterone rhythm may promote, presumably through its antagonism of the 5HT2C receptor, progenitor cell mitosis in the dentate gyrus. More recently, Dagyte *et al*[76], found that chronic stress increased total SynI (a regulator of synaptic transmission and plasticity) expression in all layers of the medial prefrontal cortex, whereas agomelatine treatment administered for 3 wk eliminated some of these effects. Chronic agomelatine administration reduced the fraction of phosphorylated SynI in all layers of the medial prefrontal cortex as well as selectively in the outer and middle molecular layers of the hippocampal dentate gyrus.

Chronic agomelatine, but not fluoxetine, increased survival of newly formed cells in the ventral part of the hippocampus without changing their phenotypic differentiation into neurons but promoting cell proliferation and BDNF messenger RNA (mRNA) expression. Molteni *et al*[80] showed that the expression of BDNF mRNA lev-

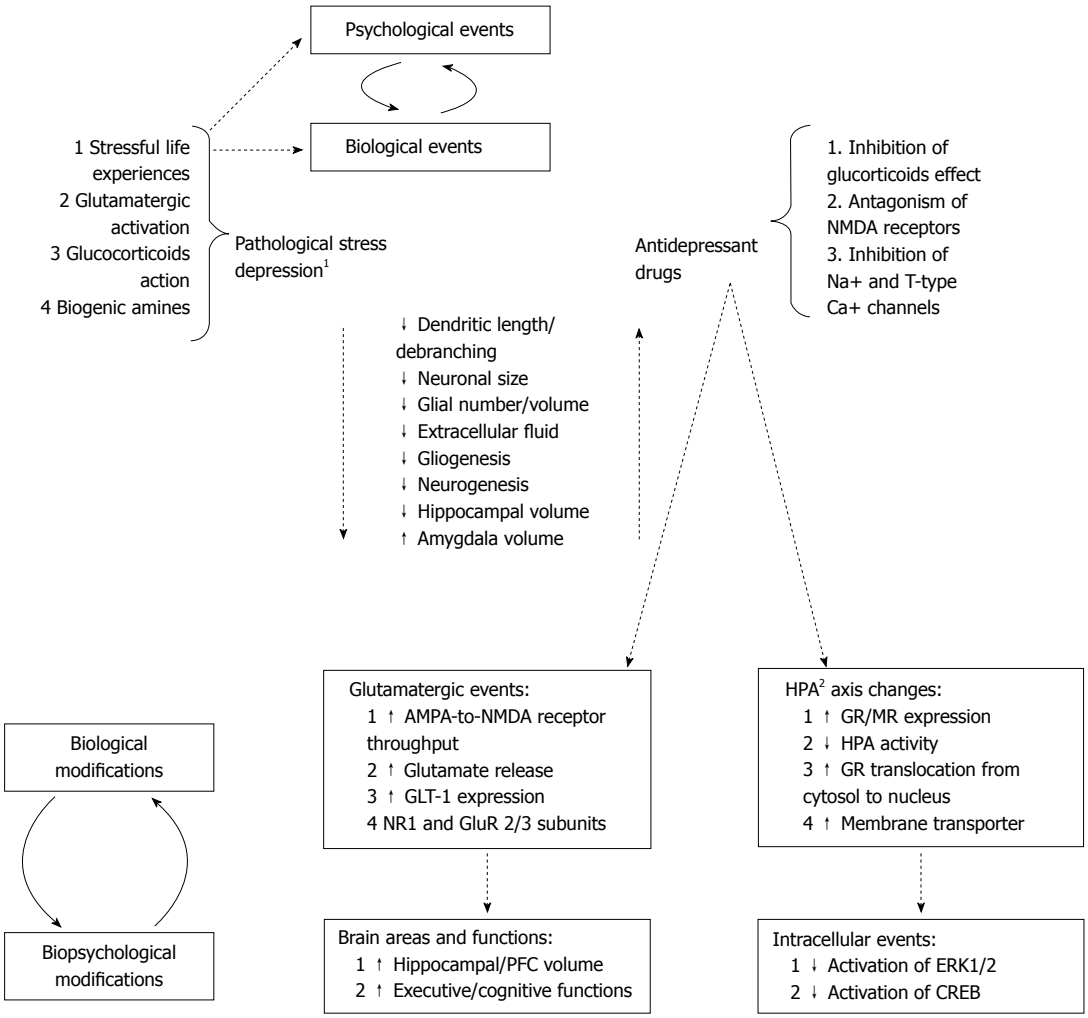

Figure 1 Proposed mechanisms leading to structural and functional modifications underlying pathological stress and major depression and the effect of antidepressant drugs on the most relevant stress-induced changes. [1]Source: Modified by[28,81]; [2]HPA: Hypotalamic pituitary axis.

els in the prefrontal cortex may be up-regulated preventing the circadian down-regulation of the neurotrophin after acute injection of agomelatine presumably through functional interaction between melatonergic MT1/MT2 and serotonergic 5-HT2C receptors. Additionally, Calabrese *et al*[81], investigating the effects on mRNA and BDNF protein expression of chronic agomelatine treatment compared to those of venlafaxine, found that only agomelatine produced major transcriptional changes in the hippocampus and increased levels of BDNF in the hippocampus and prefrontal cortex. Considering the different effect on mRNA levels and the similar cumulative effects on BDNF levels in the hippocampus and prefrontal cortex, the authors suggested that different modulatory mechanisms were induced in the two brain regions by agomelatine.

Additionally, recent studies have shown that glucocorticoids are involved in the neurogenic action of ADs[82,83]. The potential role of glucocorticoids in antidepressant-induced neurogenesis is consistent with the evidence that ADs regulate the function of the glucocorticoid receptor (GR)[84-88]. In a recent study[88], it has been identified for the first time that antidepressant-induced changes in neurogenesis are dependent on the GR. The antidepressant sertraline enhances neuronal differentiation and promotes neuronal maturation of human hippocampal progenitor cells through a GR-dependent mechanism associated with GR phosphorylation *via* protein chinase-A signalling. The authors concluded that this effect is observed only when sertraline is present during the proliferation phase, but suggested a complex regulation of neurogenesis mediated by ADs, with different GR-dependent mechanisms leading to enhanced cell proliferation without changes in neuronal differentiation, or enhanced neuronal differentiation in the presence of decreased cell proliferation.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Pathological stress and major depression are associated with loss of dendritic spines, dendritic atrophy and loss of synapses, decrease of glial cells (both in number and size) in the hippocampus and prefrontal cortex. Consequently, the hippocampus, prefrontal cortex, and re-

lated downstream structures resulted impaired non only structurally but also in functioning. Pathological stress is also associated with increased dendritic arborisation and formation of new synapses in the amygdala showing an increased volume and an abnormal functioning. The site-specific neurohistological changes explain most of depressive clinical correlates such as anhedonia, loss of motivation, anxiety, fear, and other cognitive dysfunctions. During the last decades, the neurotrophic hypothesis of depression together with the demonstration of ADs to reverse neuroplasticity and neurogenesis modifications induced by chronic stress emerged. Figure 1 summarized the most relevant structural and functional modifications of neural circuits induced by pathological stress and depression as well as modifications/adaptations induced by ADs.

Actually, our knowledge do not allow to conclude whether neuroplasticity and neurogenesis modifications represent the cause or the result of neuropathological processes related to major depression. Another criticism is that the neurotrophic theory is not able alone to explain some experimental findings regarding why ketamine[89,90], scopolamine[91,92] and electroconvulsive shock therapy[93] exert antidepressant properties. Glutamate (NMDA and AMPA receptors activation) is thought to play a crucial role in morphological changes regulating neuroplasticity. Depressive illness and stress-related modifications may affect glutamate receptors and the glutamatergic neurotransmitter system; these alterations, however, may be reversed by the administration of modern ADs. As suggested by Kasper and McEwen[15], ADs may reverse structural and functional modifications underlying depression promoting neuroplasticity mechanisms and presumably with the final result to prevent the illness progression.

Overall, ADs may reverse the stress-induced loss of neuronal cells by reducing the retraction of hippocampal neurons (neuroplasticity) or increasing cell survival and functions (neurogenesis). Also, ADs may reverse the structural and functional consequences of stress in a site-specific manner in both the hippocampus and prefrontal cortex, but not in the amygdala. This presumably explains why, although most of depressive clinical manifestations may be reversed with the administration of ADs, the vulnerability to stress instead remains[94] providing a rationale for the required maintenance of antidepressant therapy after the successful initial treatment of depression. Future longitudinal studies including larger samples of subjects should deeply investigate the potential of ADs as long-term modulators of neuroplasticity and neurogenesis mechanisms, allowing a more detailed understanding of the pathophysiology of major depression.

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World Journal of Psychiatry

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World J Psychiatr 2012 June 22; 2(3): I
ISSN 2220-3206 (online)

Acknowledgments to reviewers of *World Journal of Psychiatry*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

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World J Psychiatr 2012 June 22; 2(3): I
ISSN 2220-3206 (online)

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January 19-22, 2012
The 64th Annual National Congress of The Indian Psychiatric Society
Kochi, Kerala, India

January 20-21, 2012
AACAP 2012 Psychopharmacology Update Institute
Child and Adolescent Psychopharmacology: Integrating Current Data into Clinical Practice
Sheraton New York Hotel and Towers, New York, United States

Februrary 08-11, 2012
Thematic Conference of the World Psychiatric Association
Granada

Februrary 09-10, 2012
14th National Conference: Dementias 2012
London, United Kingdom

February 9-12, 2012
New Zealand Association of Psychotherapists Conference 2012
The Face of the Other
Victoria University, Wellington, New Zealand

February 18, 2012
Inaugural RANZCP Symposium on Youth Mental Health
Mantra on Russell, Melbourne, Australia

Februrary 23-24, 2012
Ⅱ Annual Meeting on Therapeutics in Psychiatry
Barcelona, Italy

February 23-24, 2012
Voices VIC 2012 Conference
Voices, Conversations & Transformations – Diverse Approaches to Recovery
Storey Hall, RMIT University, Melbourne, Australia

February 23-25, 2012
American Psychosocial Oncology Society 9th Annual Conference
Miami, FL, United States

February 29, 2012
Conjoint Medical Education Seminar
Hilton on the Park, Melbourne, Australia

March 3-6, 2012
20th European Congress of Psychiatry
Prague, Czech Republic

March 16-19, 2012
2012 American Association for Geriatric Psychiatry Annual Meeting
Washington, DC, United States

March 17, 2012
Body In Mind 2012
AMREP Centre, Alfred Hospital, Melbourne, Australia

March 21-24, 2012
American Neuropsychiatric Association 23rd Annual Meeting
New Orleans, LA, United States

March 21-25, 2012
American Counseling Association 2012 Annual Conference & Exposition
San Francisco, CA, United States

March 23-24, 2012
Psychiatric Society of Virginia 2012 Spring Meeting
Richmond, VA, United States

March 27-31, 2012
5th Annual Psychopharmacology Institute and ISPN Annual Conference - International Society Of Psychiatric-Mental Health Nurses
Atlanta, GA, United States

April 11-14, 2012
33rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine
New Orleans, LA, United States

April 12-15, 2012
2012 Anxiety Disorders Association of America Annual Conference
Arlington, VA, United States

April 16-18, 2012
Australian & New Zealand Disaster and Emergency Management Conference
Brisbane Convention Centre, Australia

April 18-21, 2012
45th American Association of Suicidology Annual Conference
Baltimore, MD, United States

April 23-26
Freedom and Recovery: Integrated Mental Health and Addiction Treatment for Service Members
San Diego, CA, United States

May 2-4, 2012
ANZSGM Annual Scientific Meeting 2012
Dementia: Managing Not to Forget
Hilton Hotel, Sydney, Australia

May 5-9, 2012
2012 American Psychiatric Association Annual Meeting
Philadelphia, PA, United State

May 20-24, 2012
RANZCP 2012 Congress
Hobart, Tasmania, Australia

June 14-17, 2012
American Psychiatric Nurses Association 9th Annual Psychopharmacology Institute
Reston, VA, United States

July 6-8, 2012
RANZCP Queensland Branch Weekend Conference
Hyatt Regency Coolum, Australia

July 7-10, 2012
Society For Developmental and Behavioral Pediatrics 2012 Annual Meeting
Phoenix, AZ, United States

July 10-13, 2012
International Congress of the Royal College of Psychiatrists
BT Convention Centre, Liverpool, United Kingdom

August 6-8, 2012
13th International Mental Health Conference
Outrigger Inn, Gold Coast, Australia

September 4-7, 2012
Faculty of Forensic Psychiatry Conference
Hong Kong Academy of Medicine, Hong Kong, China

September 7-11, 2012
International Psychogeriatric Association International Meeting 2012 (Jointly Hosted By the RANZCP Faculty of Psychiatry of Old Age)
Cairns, Queensland, Australia

September 13-16, 2012
American Association For Marriage And Family Therapy Annual Conference 2012
Charlotte, NC, United States

September 27-29, 2012
2nd International Congress on Borderline Personality Disorder and Allied Disorders
Match research, need and demand to treatment and resources
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October 1-3, 2012
Ranzcp Section of Psychotherapy 2012 Conference
Monash University Centre, Prato, Italy

October 3-5, 2012
RANZCP Faculty of Child and Adolescent Psychiatry Annual Meeting
Novotel Manly Pacific, Sydney, Australia

October 4-7, 2012
64th Institute On Psychiatric Services
New York, NY, United States

October 13-14, 2012
RANZCP Victorian Branch Conference 2012
RACV Healesville Country Club, Australia

October 17-20, 2012
International Convention Of Pan-American Medical Women´s Alliance
Guadalajara, Mexico

October 21-24, 2012
ISQua 29th International Conference
Geneva, Switzerland

November 7-10, 2012
American Psychiatric Nurses Association 26th Annual Conference
Pittsburgh, PA, United States

November 8-11, 2012
International Conference on Clinical Practice in Alzheimer Disease
Budapest, Hungary

November 20-23, 2012
Silent Witnesses: The Place of Coronial System in A Civilised Society (Asia Pacific Coroners' Society)
Amora Hotel, Sydney, Australia

November 22-25, 2012
The 2nd International Multidisciplinary Forum on Palliative Care
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November 10-12, 2012
CHADD 23rd Annual International Conference on ADHD - Children and Adults with Attention Deficit/Hyperactivity Disorder
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World J Psychiatr 2012 June 22; 2(3): I-V
ISSN 2220-3206 (online)

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ISSN

ISSN 2220-3206 (online)

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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Conference paper

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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