The 29th Annual Meeting of the Canadian College of Neuropsychopharmacology

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The 29th Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) was held in Chicago, Illinois, July 9–13, 2006, in conjunction with the international organization, the Collegium Internationale Neuro-Psychopharmacologium (CINP). This report summarizes the 3 CCNP award lectures and 4 symposia.

Award lectures

CCNP Heinz Lehmann Award lecture

Dr. Trevor Young (University of Toronto, Toronto) gave the 2006 Heinz Lehmann Award lecture entitled “Towards an understanding of the treatment of bipolar disorder.” As Dr. Young described, an increasing number of drugs with mood-stabilizing function are being used in the treatment of bipolar disorder, but the mechanisms mediating their therapeutic effects remain unclear. One focus of Dr. Young’s work has been to investigate the possibility that their mood-stabilizing effects are mediated through neuroprotective mechanisms. This hypothesis stems from evidence showing neuronal damage and neuronal loss in postmortem brains of patients with bipolar disorder. Dr. Young showed data from a variety of in vitro and in vivo studies in laboratory animals that demonstrate that mood stabilizing drugs, such as lithium, valproate and atypical antipsychotics, do prevent cell damage and cell loss. These neuroprotective effects appear to be mediated through drug-induced alterations in the signalling transduction pathways involved in cell death and cellular plasticity. Lithium, for instance, activates survival pathways, decreases expression of pro-apoptotic genes and increases expression of anti-apoptotic genes. In addition, both lithium and valproate protect significantly against oxidative stress and, therefore, against excitotoxicity. He also showed that, in rodents, lithium and valproate prevent the chronic stress-induced reduction in dendritic arborization typically observed in the hippocampus and amygdala. In the last part of his talk, Dr. Young mentioned clinical evidence supporting the idea that treatment with a mood-stabilizing drug leads to neuroprotection. Finally, he pointed out the need for more studies to establish a link between the neuroprotective and therapeutic effects of mood-stabilizing drugs.

CCNP Innovations Award lecture

Dr. Rachel Tyndale (University of Toronto, Toronto) gave this year’s CCNP Innovations Award lecture. In her talk, entitled “Novel regulation and functions for drug metabolizing enzymes in the brain,” she discussed a family of cytochrome P450 (CYP) enzymes and their roles in regulating drug use. Although CYP 450 enzymes are usually associated with liver functions, they are also present in the brain. They are highly localized, carefully regulated, functional and responsive to drugs. Dr. Tyndale’s talk focused on the following 3 enzymes: 1) CYP2B6. People with slow metabolizing variants of CYP2B6 are less likely to start smoking and more likely to quit. Expression of this enzyme varies throughout the brain, and cigarette smokers have increased expression in certain regions, such as the cerebellar purkinje cells and the hippocampus. Smoking behaviour appears to interact with genotype to regulate expression of CYP2B6. Nicotine can induce brain-region specific expression of CYP2B6 but does not appear to occur in the liver. Induction of CYP2B1 by nicotine increases the inactivation of the central anesthetic propofol.

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The level of CYP2B1 in a brain region will modify the effects of some clinically useful drugs, and behaviour such as smoking can alter the levels of CYP2B1.

2) CYP2D. Genetic fast versus slow metabolizers appear to differ in several personality traits, including increased psychic anxiety and decreased socialization in slow metabolizers. These slow metabolizers appear to be protected from opiate dependence; however, they might be at increased risk of developing Parkinson’s disease, and slow metabolizing animals are more sensitive to the Parkinsonian effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). CYP2D levels correlate with dopamine transporter availability in the striatum. Because smokers are at lower risk of developing Parkinson’s disease, Dr. Tyndale explored a connection between nicotine and CYP2D. Smokers have increased CYP2D6 expression in some brain regions, and increased brain expression is inducible by nicotine in monkeys. CYP2D6 may play a role in preventing the development of Parkinson’s through the inactivation of toxins. People with high levels of CYP2D6 through induction by nicotine or genetics may be protected.

3) CYP2E1. This enzyme may mediate an important interaction between tobacco smoking and alcohol drinking. Alcohol and cigarettes are often consumed together, and smokers have faster alcohol elimination rates. Nicotine increases alcohol self-administration in animal models. The CPY2E1*1D induction variant increases the risk of both alcohol and nicotine dependence. Expression of CYP2E1 is increased in the rat liver and brain by both ethanol and nicotine. In humans, CYP2E1 activity as indexed by clearance of chlorozoxazone is increased after smoking. These data suggest that CPY2E1 might play a role in alcohol dependence, nicotine dependence and co-administration of these drugs.

Dr. Tyndale concluded by suggesting that the central actions of the CYP family can play a role in altering drug levels to different extents across brain regions, contribute to metabolic tolerance and cross tolerance, and either promote or prevent toxic or mutagenic effects of drugs.

CCNP Young Investigator Award lecture

The winner of this year’s CCNP Young Investigator Award was Dr. Stanley Floresco (University of British Columbia, Vancouver). The title of his talk was “Dopamine regulation of limbic-striatal interplay.” Dr. Floresco first reviewed the dopaminergic and glutamatergic inputs into the nucleus accumbens from such limbic regions as the basolateral amygdala (BLA), hippocampus, ventral tegmental area (VTA) and prefrontal cortex (PFC). Dopamine (DA) release can occur in 2 major patterns. Glutamatergic inputs from the PFC to the DA cell body can elicit DA burst firing and the phasic release of massive concentrations of DA, most of which is taken back up into the cell by the DA transporter within 100 ms. Tonic DA release, in comparison, is characterized by slow, irregular firing, leading to increased extracellular concentrations that last seconds to minutes and escape the synaptic cleft. Long-lasting, impulse-independent increases in accumbens DA release can be elicited from glutamatergic inputs from the BLA and ventral subiculum of the hippocampus. The accumbens’ neural response to this input from the BLA and subiculum is further modulated by the coincident activation of DA D1 and N-methyl-D-aspartate (NMDA) receptors.

Dr. Floresco’s next set of experiments investigated whether activity in the BLA and subiculum pathways to the accumbens affected each other. Hippocampal stimulation was found to increase hippocampal input but suppress BLA input, while dual hippocampal–BLA stimulation augmented both hippocampal and BLA input. This effect is dependent on the timing of DA release relative to the activity in each pathway, whereby if an input is active when DA is released, that input will be suppressed, but if an input is inactive when DA is released, that input will be augmented. Finally, Dr. Floresco presented data showing that inhibition of the ventral pallidum increased DA neuronal population activity but did not affect burst firing. Conversely, activation of the pedunculopontine nucleus increased DA neuron burst firing but did not affect population activity. He concluded by proposing that the DA system is compartmentalized into synaptic (phasic) and extrasynaptic (tonic) DA release. Phasic DA release, he proposed, may be important for reward-related learning, whereas tonic DA release may be important in modulating the influence of inputs to the nucleus accumbens.

Symposia

Molecular genetics of neurodevelopment in schizophrenia (Chair: Dr. Remi Quirion, McGill University, Montréal)

Dr. Lalit Srivastava (McGill University, Montréal) opened the session with a talk entitled “Behavioural and molecular changes in animals with developmental hippocampus damage or dysbindin mutation.” In the first of these 2 potential animal models of schizophrenia, rats receive neonatal lesions of the ventral hippocampus (NVHL). As adults, these rats exhibit multiple behavioural disturbances, including cognitive and sensorimotor deficits. Recent evidence suggests that a critical factor for the development of these behavioural alterations is the reorganization of neural circuitry within the prefrontal cortex (PFC). For example, Dr. Srivastava’s studies indicate that PFC pyramidal neurons of adult NVHL rats have reduced dendritic length and dendritic spine density. Moreover, by using DNA microarray analysis on PFC of adult rats with NVHL, he found that the expression of genes known to be involved in dendritic spine formation, including Homer 2, is altered. In the second part of his talk, Dr. Srivastava presented results from ongoing studies with dysbindin-1–deficient Sandy mice. Polymorphisms in the dysbindin-1 gene have been associated with schizophrenia, and reduced dysbindin-1 mRNA and protein expression have been observed in the PFC and hippocampus of the postmortem brain of subjects with schizophrenia. Dr. Srivastava showed that, although there are no differences in gross appearance between sdy/sdy and wild-type mice, adult sdy/sdy and sdy/+ mice show striking behavioural impairments that are relevant to schizophrenia, in-
cluding deficits in prepulse inhibition and increased sensitivity to locomotor activating effects of stimulant drugs. The mechanisms mediating these effects remain unclear, but preliminary results from Dr. Srivastava’s molecular studies suggest that dysbindin-1 is involved in regulating glutamatergic neurotransmission.

Dr. Michael O’Donovan (Cardiff University, Wales, UK) gave a talk entitled “Genetic analysis supports a primary abnormality in oligodendrocyte function in schizophrenia.” There is increasing evidence of abnormalities in oligodendrocyte function and myelination in schizophrenia. To explore this possibility further, Dr. O’Donovan has been using gene association analyses studies. A case-control study was summarized, showing that OLIG2, a gene critically involved in the development and differentiation of oligodendrocyte development and differentiation, has several single nucleotide polymorphisms (SNPs) associated with schizophrenia. The expression of 2 genes implicated in oligodendrocyte function, CNP and erbB4, correlates with the expression of OLIG2 in the human and the mouse brain. Both CNP and erbB4 have been previously demonstrated to have a modest association with schizophrenia. Further, using interaction analysis, he found that OLIG2 has possible epistatic effects with both CNP and erbB4. This was further supported by studies conducted with mice showing that OLIG2 regulates CNP expression and vice versa. Taken together, these findings provide further evidence for a role of alterations in oligodendrocyte development and function in the etiology of schizophrenia.

Dr. Nuria Flames (Universidad Miguel Hernández, Alicante, Spain) delivered a talk entitled “Short- and long-range attraction of cortical GABAergic interneurons by neuroregulin-1.” GABAergic interneurons are critical for proper function of the cerebral cortex. During development, these interneurons are born in subcortical regions from where they migrate long distances to reach the cortex. Dr. Flames talked about her recent work showing that neuroregulin-1 (NRG-1), a protein implicated in the pathophysiology of schizophrenia, plays a major role in controlling interneuron migration. She showed that NRG-1 isoforms are expressed in the developing cortex and, specifically, in the ‘path’ that cortical interneurons follow to reach the cortex. Moreover, a population of the migration interneurons appears to express the NRG-1 receptor ErbB4. Importantly, her results from in vitro and in vivo studies demonstrate that 1) migrating interneurons that express ErbB4 are attracted by NRG1 in a short- and long-range manner and 2) impaired ErbB4/NRG-1 function results in abnormal migration and, in turn, in reduced number of interneurons in postnatal cortex. These findings provide strong evidence that alterations in NRG-1 function during development lead to significant changes in GABAergic interneuron migration to the cortex.

In his talk entitled “Schizophrenic genes and neurodevelopmental mechanisms: starting with DISC1,” Dr. Daniel Weinberger (National Institute of Mental Health, Bethesda, Md.) critically reviewed current research on susceptibility genes in schizophrenia, particularly those that are implicated in brain development. He noted that major sources of controversy in the field include questions about the validity of genetic association studies, the real impact that genetic variations have on gene function, what mechanisms of brain development are relevant to schizophrenia, and the reason why onset is late in life. Despite the difficulty of these questions, Dr. Weinberger proposed that we might have made more progress than is sometimes suggested. For instance, allelic heterogeneity, found in genes associated with schizophrenia (e.g., DISC1), has often been regarded as an unsolvable problem intrinsic to genes associated with complex diseases. However, allelic heterogeneity appears to be the rule for genes involved in Mendelian disorders (e.g., the CFTR gene in cystic fibrosis), and complex disease genes are not likely to be different. Similarly, although results from genetic association studies can be regarded as showing only inconsistent alleles and haplotypes, the variability could also be interpreted as evidence that, for some genes, the genetic associations are exceptionally complicated. A compelling example is the COMT gene for which multiple functional SNPs have been identified. In terms of identifying developmental mechanisms that are relevant to schizophrenia, the most promising strategy may be to exploit cellular and animal models. Viewed from this perspective, he proposed, the search for genes involved in schizophrenia is arguably one of the most successful efforts in complex medical genetics. The best examples, he suggested, are studies on DISC1 and Neuroregulin1 genes. Both genes, and the ones they interact with, seem to be involved in specific neurodevelopmental processes. In turn, the genes tell us what the disorder is at a cellular level. Taken together, the current evidence in schizophrenia points to alterations in synaptic processing and in brain development. This optimism noted, he stressed that the characterization of pathogenetic pathways derived from susceptibility genes will require deep understanding of genetic variation, gene processing, molecular pathways and the interacting environment.

Advances in neurobiology, assessment and treatment of female-specific mood disorders (Chair: Dr. Meir Steiner, McMaster University, Hamilton, Ont.)

Dr. Meir Steiner (McMaster University, Hamilton) discussed the prominent occurrence of irritability in a wide range of mood and anxiety disorders. In female-specific mood disorders (e.g., premenstrual dysphoric disorder, postpartum depression), it is the number one complaint at presentation and appears to respond particularly well to treatment with serotonin reuptake inhibitors. Some recent evidence suggests that the occurrence of irritability in premenstrual syndrome is linked to the s allele of the gene that encodes for the serotonin transporter. Despite these intriguing observations, there has been surprisingly little research about irritability, and a scale to measure it objectively has not been available. To this end, Dr. Steiner and his colleague Dr. Born have developed a new questionnaire, the Born–Steiner Irritability Scale (BSIS). This BSIS focuses on 5 features: annoyance, anger, tension, hostile behaviour and sensitivity. Recent testing indicates that the BSIS has excel-
lent inter-item correlations, internal consistency and test–retest reliability. Two versions have been developed: a 14-item Self-Rating version and a 5-item Clinician-Rating version. Both versions are easy to administer, and they may become the starting point for the objective study of irritability as a clinical phenomenon.

Dr. Claudio Soares (McMaster University, Hamilton) began his presentation by noting that, starting from puberty, rates of mood disorders are higher in women than in men. This sex difference becomes greater again at age 50, at which point rates of depression become more common in women and less common in men. An estimated 3–9% of women meet criteria for premenstrual dysphoric disorder (PMDD), 20–40% for premenstrual syndrome, and 60–75% for mild premenstrual symptoms; 10–15% experience postpartum depression. The menopausal transition is also a period of increased risk for depression, even in the absence of past episodes. The presence of “hot flashes” predicts increased risk, as does a history of adverse life events. Although gonadal hormones are implicated, the exact neurobiological mechanisms remain poorly understood. For example, it remains unclear whether PMDD reflects abnormal gonadal hormone release or an abnormal response to normal release. Selective serotonin reuptake inhibitors (SSRIs) exhibit excellent and rapid clinical efficacy, but there is evidence that the mechanism of action is not directly related to serotonin. The risk for a menopause-related mood disorder and associated symptoms can be reduced by hormone replacement therapy (HRT) and treated with SSRIs and hypnotics.

Dr. Teri Pearlstein (Brown Medical School, Providence, RI) provided a comprehensive review of treatments for female-specific mood disorders. It is now confidently established that luteal phase treatment with selective serotonin and serotonin-norepinephrine reuptake inhibitors (SNRIs) is effective for PMDD. Withdrawal symptoms are not evident unless high doses are used. Women with severe PMDD might benefit from continuous dosing, and this decision should be made on a case-by-case basis, depending on the patient’s symptom severity and withdrawal response. Alternative treatments include oral contraceptives, ovulation suppression treatments and oophorectomy/hysterectomy. With respect to treating women for mood disorders during pregnancy, in general, the consensus remains that the potential detrimental consequences of not treating the depression are greater than those associated with treating it. Approximately 30% of infants exhibit a mild “neonatal adaptation” syndrome (jitteriness, irritability, decreased affect expressivity), but this is transient. Major congenital malformations have not been reported, with the possible exception of paroxetine. However, SSRIs might slightly increase the risk of miscarriage and hypertension. There is no evidence of long-term adverse effects of neonatal SSRI exposure, although this has yet to be thoroughly studied. In comparison, follow-up studies of children of women with depression during pregnancy indicated a higher rate of behavioural problems at age 8–9 years. Benzodiazepines and lithium appear to be relatively safe, although other mood stabilizers may have more risks (e.g., carbamazepine, valproate). One solution, Dr. Pearlstein noted, is that there are effective nonpharmacological treatments for mood disorders, such as psychotherapy and phototherapy.

Recent advances in the neuropharmacology of motivation and emotion (Chair: Dr. Andrew Greenshaw, University of Alberta, Edmonton, Alta.)

Dr. George F. Koob (the Scripps Research Institute, La Jolla, Calif.) gave a lecture entitled “Neurobiology of addiction: neuroadaptational mechanisms from the dark side.” He began by suggesting that the early stages of drug use share similarities with impulse control disorders, but that the “dark side” of drug dependence develops, features of a compulsive disorder become more prominent. In this phase, drug use is motivated by alleviating withdrawal and negative affect as well as an obsessive preoccupation with drug taking. Dr. Koob proposed that the extended amygdala (comprising the central and medial nuclei of the amygdala, the medial and lateral bed nuclei of the striata terminalis and the shell of the nucleus accumbens) may be the primary mediator of these motivational changes in the development of addiction. Changes to dopamine, opioid peptides, serotonin and gamma-aminobutyric acid (GABA) may mediate the positive hedonic effects of drug use, as well as the negative effects of withdrawal. With increased drug use, these substances may lose their ability to produce a positive hedonic response. In combination with increases in other transmitters, such as corticotropin-releasing factor (CRF), decreased levels of these substances might form part of an “antireward” system that drives the shift from impulsive to compulsive drug use. CRF may be an important part of this “antireward” system, because within the central nervous system, it promotes arousal and induces stress-like responses and aversive dysphoric states. CRF antagonists and knockouts can blunt the reinstatement of drug taking after stress or during withdrawal in animal models. Even in the absence of withdrawal or stressors, CRF antagonists appear to specifically and dose-dependently decrease alcohol self-administration in dependent animals both when injected subcutaneously and when injected directly into the central nucleus of the amygdala. CRF levels in the extended amygdala increase during the development of dependence, and CRF antagonists appear to be effective in suppressing drug-taking behaviour. Dr. Koob concluded by suggesting that the decreases in reward system function and in the recruitment of antireward systems during the development of dependence contribute to the compulsive drug seeking seen in addiction.

Dr. Klaus A. Miczek (Tufts University, Medford, Mass.) gave a talk entitled “Escalated aggression: GABA, interaction with 5-HT receptor subtypes in the corticolimbic system.” Dr. Miczek began by suggesting that the original adaptive purposes of aggressive behaviour (social dominance, territorial defence) have been de-emphasized in our societies and that aggressive behaviour is now expressed more pathologically. This impulsive-aggressive behaviour is
readily provoked, appears at a high rate and intensity and is difficult to terminate. Neurobiologically, impulsive aggression appears to be influenced by exposure to or anticipation of violence, which results in decreased cortical serotonin and increased dopamine in the nucleus accumbens and prefrontal cortex. Exposure to aggression appears to be much more stressful for socially subordinate animals. Both serotonin-1A knockout mice, and 5-hydroxytryptamine (HT), antagonists promote aggressive behaviour, whereas agonists suppress it. This effect appears to be mediated through somatodendritic autoreceptors in the raphe nucleus. Alcohol and other positive modulators of gamma-aminobutyric acid (GABA), receptors heighten aggressive behaviour, and GABA, α, subunit antagonists can decrease aggression. 5-HT receptor agonists, primarily acting in prefrontal areas, can reduce aggression instigated both by alcohol and by social challenge. However, some 5-HT agonists produce either no change or decreases in aggressivity when administered alone but lead to increases in aggressive behaviour when combined with alcohol. Dr. Miczek concluded by suggesting that 5-HT receptors in the prefrontal cortex are potent mediators of aggressive behaviour, which in turn, are potently modulated by GABA receptors.

Dr. Richard J. Beninger (Queens University, Kingston) gave a talk entitled “Molecular mechanisms of reward-related incentive motivational learning.” Dr. Beninger presented data suggesting that dopamine mediates the establishment but not the expression of reward-related incentive learning (IL). Similarly, blockade of cAMP dependent protein kinase (PKA) in the nucleus accumbens can prevent the acquisition but not the expression of IL in tests of conditioned activity and conditioned place preference (CPP). Dr. Beninger then elaborated on intracellular mechanisms required for IL. He suggested that protein kinase C (PKC), the mitogen activated protein kinases (MAPKs) extracellular regulated kinase (ERK) 1/2 and p38, but not the jun n-terminal kinase (JNK), are required to establish CPP to amphetamine. Inhibition of calcineurin (CN) in the accumbens also promotes the establishment of CPP. However, preliminary evidence suggests that the exchange protein activated by cAMP (EPAC) is not critical for CPP. Glutamate is also involved in IL, and NMDA receptors may be primarily involved in establishing IL, whereas AMPA receptors appear to be critical only in the expression of IL. Dr. Beninger proposed that the dynamic interaction of dopamine and glutamate in the striatum through these pathways promotes IL via dopamine-mediated changes in glutamate receptor effectiveness. He then described abnormalities in this intracellular signalling cascade in the striatum of patients with schizophrenia. He proposed that some of their symptoms might arise from an excess of IL and that treatments aimed at these signalling molecules might prove to be effective.

Dr. Anthony Phillips (University of British Columbia, Vancouver, BC) gave a talk entitled “Dysphoria induced by withdrawal from repeated exposure to psychostimulant drugs represents motivational but not hedonic effects.” Dr. Phillips suggested that withdrawal from psychostimulant drugs shares many features with major depression, including somatic and psychological symptoms. Tolerance of striatal dopamine efflux to repeated doses of amphetamine can be demonstrated, and efflux remains low during withdrawal. In a model of withdrawal following repeated amphetamine exposure, rats showed reductions in striatal dopamine efflux during the preparatory but not consummatory phases of sucrose solution ingestion. They also show reduced willingness to work for sucrose. Similarly, amphetamine withdrawal suppresses anticipatory sexual behaviour and increases post-ejaculatory intervals but does not affect sexual behaviour during copulation. During amphetamine withdrawal, animals were less willing to work for intracranial self-stimulation (ICSS); electroconvulsive therapy partially restored this behaviour. When animals that are responding for a 32% sugar solution are switched to a 4% solution, their willingness to work for the solution drops below that of animals maintained at 4%. Animals in amphetamine withdrawal show larger reductions. Similarly, when switched from 4% to 32%, animals in withdrawal showed blunted increases in responding. Dr. Phillips concluded by suggesting that withdrawal preferentially impacts preparatory rather than consummatory behaviours. He suggested that the suppression of striatal dopamine seen in amphetamine withdrawal may be an important correlate of the depressive symptoms, particularly motivational abnormalities, seen in humans.

Treatment-resistant depression: “differential diagnosis” and newer treatment strategies (Chair: Dr. Robert P. Kraus, Royal Ottawa Hospital, Ottawa)

Dr. Robert Kraus (Royal Ottawa Hospital, Ottawa) gave the first talk, entitled “Medical factors associated with treatment-resistant depression.” Up to 70% of people treated with antidepressant drugs do not achieve full remission. Some possible determining factors that contribute to antidepressant treatment failure include other medical illness, such as hypothyroidism, and other hormonal or metabolic disorders; sleep apnea; drug use/abuse; comorbid but undiagnosed psychiatric disorders; subtypes of major depression, such as atypical or double depression and unappreciated bipolar disorder. Rapid metabolism of antidepressant drugs by genetic variants of drug metabolizing cytochrome P450 enzymes (e.g., CYP2D6) resulting in chronic underdosing may also be a significant contributing factor. Dr. Kraus then presented data from a prospective study of 260 patients with depression whose laboratory results for thyroid function, vitamin B12, prolactin and testosterone were analyzed. Eighty-eight percent of the patients had at least one metabolic abnormality that could potentially contribute to depressive symptoms. The most notable deficiencies were for vitamin B12 (15% had levels less than 150 pM) and free testosterone (34% of patients). As well, 14% of patients had a significantly increased prolactin level. Excess prolactin has been shown to be associated with psychotic symptoms. Dr. Kraus concluded that most patients presenting with treatment-resistant depression were identified as having other medical factors known to contribute to treat-
ment failure. Identifying and correcting these factors may result in greater remission rates.

The second talk was given by Dr. K. Ranga Krishnan (Duke University, Durham, SC), entitled “White matter hyperintensity progression and late-life depression outcomes.” Subcortical ischemic disease (SID), characterized by white matter hyperintensities in the parenchyma, is common in the elderly and seems to be associated with late-onset or geriatric depression. In a study of 133 elderly (over age 60 years) subjects meeting DSM-IV criteria for major depression, Dr. Krishnan and colleagues performed MRI scans at baseline and again in 2 years time. In the subjects who had sustained remission from depression during that time, the increase in white matter hyperintensities was significantly less than in those subjects who did not achieve remission. Further, large increases in white matter intensities were significantly associated with failure to achieve remission. He concluded his talk by noting that greater progression of white matter hyperintensities is associated with poorer outcomes in geriatric depression.

The talk given by Dr. Russell T. Joffe (New Jersey Medical School, New Jersey, NY) was entitled, “Augmentation strategies: a critical review.” Dr. Joffe began by stating that less than one-half of depression patients who receive an antidepressant drug for their acute depressive episode will have an adequate treatment response. However, there is sufficient data to support the use of an augmentation strategy for these patients. Some studies have shown efficacy with nonantidepressant compounds, such as thyroid T3 hormone, lithium, pindolol and buspirone. This strategy is different from combination therapy, which involves the simultaneous administration of at least 2 antidepressant drugs. Augmentation therapy with thyroid hormones has been know for many years to be effective, especially in women, and has been shown in a meta-analysis to be effective across different studies and in different patient populations. In another study of nonresponders to citalopram monotherapy, augmentation with bupropion resulted in a 30% remission rate, as did augmentation with buspirone. Lithium augmentation increased response rates to antidepressant therapy by 40%–60% in open-label trials.

The next speaker was Dr. Pierre Blier (University of Ottawa, Ottawa, Ont.). The title of his talk was “Serotonin-noradrenergic receptor blocker that increases norepinephrine re-release. When paroxetine and mirtazapine were co-administered, there was a remission rate of 63% after 8 weeks of treatment, compared with 25% for each drug when given as monotherapy. In another study, there was a remission rate of approximately 25% for fluoxetine alone with a number-needed-to-treat of 10. When fluoxetine was combined with mirtazapine, the number-needed-to-treat decreased to 5. Further, the dropout rate was only 15%, and there were no dropouts due to adverse drug reactions. These studies demonstrate that enhancing both norepinephrine and serotonin transmission leads to a superior antidepressant efficacy within a clinical trial protocol.

The final speaker of the symposium was Dr. Richard Shelton (Vanderbilt University, Nashville, Tenn.). The title of his talk was “Novel treatments for treatment-resistant depression.” He began by stating that an incomplete response to antidepressant treatment is the rule rather than the exception. The most common reason for an incomplete response is that the patient has not been treated with an adequate dose for an adequate period of time or has been noncompliant with the treatment. He proposed that noncompliance may be due in large part to the inadequate response. He then presented data from a study conducted by the National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression (STAR*D). In the citalopram arm of the study, there was a remission rate of 33% and a response rate of 47%. When the nonresponders to citalopram were switched to another monotherapy, the remission rate was between 18% and 25%. When they were switched to a combination therapy, remission rates increased to 30%. When subjects were given augmentation medication and cognitive–behavioural therapy, or its variant CBASP (Cognitive Behavioural-Analysis System of Psychotherapy), the remission rate increased to 48–62%. Lamotrigine augmentation produced the highest remission rate (62%), while risperidone produced the lowest (48%). Amphetamine augmentation resulted in a remission rate of 56%; lithium, 59%; and olanzapine, 58%. This study demonstrates that combination therapy, augmentation therapy, and the addition of cognitive–behavioural therapy all significantly improve remission rates in patients who do not respond to monotherapy.

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