**Depression, BD, MDD & DD**

**Venlafaxine, Elderly & DD**

*An open treatment trial of venlafaxine for elderly patients with dysthymic disorder.*

**Authors:** Devanan D, Juszcak N, Nobler MS, Turret N, Fitzsimons L, Sackeim HA, Roose SP. - New York State Psychiatric Institute, 1051 Riverside Drive, Unit 126, New York, NY 10032. dpd3@columbia.edu.


**Summary:** Treatment response and side effects of venlafaxine were evaluated in an open-label trial of elderly outpatients with dysthymic disorder (DD). Patients received flexible dose (up to 300 mg/d) venlafaxine (Effexor XR) for 12 weeks. Of 23 study patients, 18 completed the trial. Fourteen (60.9%) were responders in intent-to-treat analyses with the last observation carried forward, and 77.8% were responders in completer analyses. Nearly half the sample (47.8%) met criteria for remission. In the intent-to-treat sample, increased severity of depression at baseline was associated with superior response, and the presence of cardiovascular disease was associated with poorer response. Venlafaxine open-label treatment was associated with fairly high response rates and generally good tolerability in elderly patients with DD. These results indicate that in elderly patients with DD, placebo-controlled trials of a dual reuptake inhibitor such as venlafaxine would be needed to assess its efficacy or to compare its efficacy to that of other antidepressants.

**BD I & Olanzapine**

*Olanzapine: a review of its use in the management of bipolar I disorder.*

**Authors:** McCormack PL, Wiseman LR.- Adis International Limited, Auckland, New Zealand.

**Source:** Drugs. 2004;64(23):2709-26. Related Articles, Links

**Summary:** Olanzapine is an atypical antipsychotic that is approved in the US and Europe for the oral treatment of acute manic episodes in patients with bipolar I disorder, and for maintenance therapy to prevent recurrence in responders. Oral olanzapine is effective in the treatment of bipolar mania, both as single agent therapy and as adjunctive therapy in combination with lithium or valproate semisodium. In the treatment of acute episodes, olanzapine is superior to placebo and at least as effective as lithium, valproate semisodium, haloperidol and risperidone in reducing the symptoms of mania and inducing remission. Additional comparative studies are required to determine the efficacy of olanzapine relative to newer atypical antipsychotics, such as quetiapine, ziprasidone and aripiprazole. Olanzapine is also effective at delaying or preventing relapse during long-term maintenance therapy in treatment responders, and is currently the only atypical antipsychotic approved for this indication. Current evidence suggests that olanzapine may be more effective than lithium in preventing relapse into mania, but not relapse into depression or relapse overall. Olanzapine is generally well tolerated, and although it is associated with a higher incidence of weight gain than most atypical agents, it has a low incidence of extrapyramidal symptoms (EPS).

**Conclusion:** Therefore, oral olanzapine is a useful first-line or adjunctive agent for both the acute treatment of manic episodes and the long-term prevention of relapse into manic, depressive or mixed episodes associated with bipolar I disorder.

**Recurrent MDD & KLS**

*Koro-like symptoms in recurrent major depression.*

**Authors:** Freudenmann RW, Schönfeldt-Lecuona C.- Abt. Psychiatrie III, Universitätsklinikum Ulm

**Source:** Nervenarzt. 2004 Dec 1; [Epub ahead of print] Related Articles, Links

**Summary:** We report the case of a German male with a major depressive episode who also suffered from the terrifying perception that his penis was shrinking. These so-called koro-like symptoms (KLS) had also been present in earlier depressive episodes and subsided in the symptom-free interval of the recurrent depressive disorder. Under sufficient antidepressant medication with venlafaxine and lithium not only KLS but also the depressive symptoms remitted. **Conclusion:** The course of illness provides further evidence that KLS are not a distinct clinical entity in Western countries, but represent a concomitant syndrome that requires treatment of the underlying illness.

**BD & Therapeutic Regimens**

*Employing pharmacologic treatment of bipolar disorder to greatest effect.*

**Authors:** Schatzberg AF. From the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, Calif.

**Source:** J Clin Psychiatry. 2004;65 Suppl 15:15-20. Related Articles, Links

**Summary:** Mechanisms of action, onset and duration of action, and interactions with other medications of all of the pharmacokinetic properties of pharmacologic agents affect the efficacy and safety of therapeutic regimens for bipolar disorder. For example, antiglutamatergic agents such as lamotrigine may relieve depression but have no impact on mania. Atypical antipsychotics with the dual effect of blocking dopamine and serotonin receptors in the brain decrease psychosis, mania, and, according to some preliminary indications, possibly depression. The impact of these properties has been borne out in clinical studies. **Conclusion:** Mood stabilizers such as lithium and valproate stabilize mood by significantly decreasing the manic and hypomanic symptoms of bipolar disorder, although they can have effects on depressive symptoms too. Lamotrigine stabilizes mood by reducing depression. The atypical anti-psychotics have been shown to be effective either as monotherapy or in combination with mood stabilizers.

**Depression, Oldest & Citalopram**

*Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial.*

**Authors:** Roose SP, Sackeim HA, Krishnan KR, Pollock BG, Alexopoulos G, Lavretsky H, Katz IR, Hakkarainen H; Old-Old Depression Study Group. - New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA. spr2@columbia.edu
**Resistant Depression & Novel Antipsychotics**

*Novel Antipsychotics for Treatment-Resistant Depression*

**Authors**: by Richard C. Shelton, M.D.

**Source**: Psychiatric Times October 2004 Vol. XXI Issue 11

**Summary**: Finally, Papakostas et al. (2004) treated 20 patients who had experienced an inadequate response to an SSRI with an open trial of the addition of ziprasidone (Geodon) (maximum dose 80 mg bid) to the SSRI. Prior failures included a minimum dose of 20 mg/day of paroxetine (Paxil), fluoxetine or citalopram (Celexa), or 50 mg/day of sertraline (Zoloft) for six weeks. Thirteen of 20 patients completed the trial (65%); of the completers, 61.5% experienced a therapeutic response (50% reduction in Hamilton Depression Scale scores), and 38.5% experienced remission (HAM-D≤7). For the intent-to-treat analysis, 50% achieved response and 25% remission.

Altogether, these reports suggest that novel antipsychotics, particularly olanzapine, may produce an augmenting effect when given with an SSRI. However, at this point, the data must be considered preliminary, and more research clearly is needed before any conclusion can be reached.

**HIV-infected & Depression**

- **Depressive symptoms, neurocognitive impairment, and adherence to highly active antiretroviral therapy among HIV-infected persons.**

**Authors**: Ammassari A, Antinori A, Aloisi MS, Trotta MP, Murri R, Bartoli L, Monforte AD, Wu AW, Starace F. - Clinica delle Malattie Infettive, Universita Cattolica del Sacro Cuore, Rome, Italy. aammassari@libero.it

**Source**: Psychosomatics. 2004 Sep-Oct;45(5):394-402

**Summary**: The association of depressive symptoms, neurocognitive impairment, and adherence to highly active antiretroviral therapy (HAART) was evaluated in 135 HIV-infected persons. Thirty percent reported nonadherence to HAART. Depressive symptoms (assessed with the Montgomery-Asberg Depression Rating Scale) and neurocognitive impairment (assessed with a neuropsychological test battery) were documented in 24% and 12%, respectively, of the study participants. Nonadherence to HAART was independently associated with worse depression rating scale scores (odds ratio=4.09, 95% confidence interval [CI]=1.50-11.0), acquisition of HIV through injection of drugs (odds ratio=2.59, 95% CI=1.05-6.39), and complaints about impairment of sexual activity (odds ratio=6.62, 95% CI=1.16-37.6). The presence of depressive symptoms, but not neurocognitive impairment, was associated with nonadherence.

**Bipolar Disorder**

- **Utilization of MRS to Identify Neurochemical Abnormalities in Patients With Bipolar Disorder**

**Authors**: by Serap Monkul, M.D., and Jair C. Soares, M.D.

**Source**: Psychiatric Times August 2004 Vol. XXI Issue 9

**Summary**: Magnetic resonance spectroscopy (MRS) is a useful, noninvasive method of examining alterations in brain neurochemistry that might be associated with the development of bipolar disorder (BD) and the effects of treatment (Soares et al., 1996). It uses the same technology as magnetic resonance

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**SSRIs, Venlafaxine & Children MDD**

- **Selective serotonin reuptake inhibitor and venlafaxine use in children and adolescents with major depressive disorder: A systematic review of published randomized controlled trials**

**Authors**: Courtney DB. - Queen’s University, Kingston, Ontario. darren.courtney@sympatico.ca


**Summary**: This review critiques published randomized placebo-controlled trials pertaining to the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine in the treatment of major depressive disorder in children and adolescents. METHOD: Medline was searched for articles meeting defined inclusion criteria. The following key terms were used: depressive disorders, antidepressive agents, fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine, venlafaxine, child, and adolescent. RESULTS: Six articles met inclusion criteria. Only 2 studies claim efficacy by significant results in primary outcomes; both have since been contested in further analysis. Not one study adequately examines safety, particularly with respect to whether a link exists between antidepressant use and induction of suicidal ideation or attempts. Conclusion: Published studies on SSRI or venlafaxine use in children and adolescents are inconclusive with respect to safety and efficacy, owing to inappropriate claims of efficacy, lack of improvement in global functioning scores, nonstandardized data collection regarding adverse effects, exclusion of suicidal subjects in the recruitment process, grouping of children and adolescents together, small sample sizes, conflict of interest posed by pharmaceutical company sponsorship, and publishing bias. Future investigators should consider these factors when developing study designs.
imaging and provides a frequency signal intensity spectrum of multiple peaks that reflect the metabolite levels of a localized region in the brain. Magnetic resonance spectroscopy data are usually displayed in the frequency domain, and the area under a specific peak is proportional to the number of protons processing at that frequency (Stanley, 2002). It can assess chemicals containing phosphorus-31 (31P), carbon-13 (13C), lithium-7 and fluorine-19. The most commonly used, however, is proton magnetic resonance spectroscopy (1H-MRS).

**Depression & Escitalopram**

- **Escitalopram: better treatment for depression is through the looking glass**

**Authors:** PJ Main, SP Wengel & WJ Burke


**Summary:** Depression remains a common and often devastating illness. With the introduction of the selective serotonin reuptake inhibitors in the 1980s, patients were afforded treatment for depression that was both safer and better tolerated than any prior treatment modality offered. Although selective serotonin reuptake inhibitors quickly became the most widely used medications for the treatment of depression, no single agent has been recognized as an obvious first-line choice. Chirality potentially offers one method to improve upon the selective serotonin reuptake inhibitor class. For racemic compounds that differ in stereospecificity, separation into single enantiomers can result in significant changes in potency, tolerability and efficacy. One of the most widely prescribed selective serotonin reuptake inhibitors is citalopram, which exists as a racemic mixture of R- and S-enantiomers. The S-enantiomer escitalopram (Cipralex®, Lundbeck) is the therapeutically active portion of the parent compound and has a proven antidepressant efficacy. The R-enantiomer lacks activity as an antidepressant and has been shown to inhibit the effect of the S-enantiomer when the two are combined. Escitalopram is the most selective member of its class and with minimal effects on the cytochrome P450 system, has a negligible potential for drug–drug interactions. In placebo-controlled trials, escitalopram has consistently demonstrated symptomatic improvement as early as the first to second week of treatment. In addition to antidepressant efficacy, escitalopram also appears to exhibit significant anxiolytic properties. It has also shown efficacy in treating panic disorder and generalized and social anxiety disorders. This is advantageous as many patients who suffer from depression also experience comorbid anxiety disorders. antidepressant, binding, efficacy, enantiomer, escitalopram, major depressive disorder, selective serotonin reuptake inhibitor, serotonin tolerability, uptake.

**Depression & Rheumatoid Arthritis**

- **Impact of social support on valued activity disability and depressive symptoms in patients with Rheumatoid Arthritis.**

**Authors:** Neugebauer A, Katz PP. - University of California, San Francisco, CA 94143-0920, USA

**Source:** Arthritis Rheum. 2004 Aug 15;51(4):586-92

**Summary:** OBJECTIVE: To examine the impact of instrumental and emotional support on valued life activity (VLA) disability and depressive symptoms. Instrumental support was expected to affect VLA disability; emotional support was expected to be associated with depressive symptoms and moderate the impact of VLA disability on depressive symptoms. METHODS: Data were collected over 3 years through interviews with the University of California, San Francisco, Rheumatoid Arthritis Panel. Analyses assessed whether instrumental support predicted later VLA disability and whether emotional support predicted both concurrent and later depressive symptoms. RESULTS: Receiving adequate instrumental support was associated with less subsequent VLA disability. Strong associations were noted between both VLA disability and emotional support with concurrent depressive symptoms. No relationship was found between emotional support and later depression. No evidence was found for the hypothesis that emotional support moderated the impact of VLA disability on depressive symptoms. Conclusion: Results highlight the need to assess different types of support and their unique impact on critical outcomes. Instrumental support is beneficial to the maintenance of valued activities, a critical factor in the psychological adjustment of individuals living with rheumatoid arthritis. Emotional support has a significant short-term impact on depression, although it may not buffer the impact of VLA disability on future depression.

**BD & Levetiracetam, Monotherapy**

- **Monotherapy treatment of bipolar disorder with levetiracetam.**

**Authors:** Kaufman KR. - Departments of Psychiatry and Neurology, UMDNJ-Robert Wood Johnson Medical School, 125 Paterson Street, Suite 2200, New Brunswick, NJ 08901, USA

**Source:** Epilepsy Behav. 2004 Dec;5(6):1017-20. Related Articles, Links

**Summary:** Bipolar patients with early-onset, comorbid substance abuse, rapid cycling, and mixed episodes are difficult to treat and frequently require rational polypharmacy. When polypharmacy is unsuccessful, the clinician must consider the off-label use of newer psychotropics. Levetiracetam is a novel anticonvulsant with antikinding, inhibitory, and neuroprotective properties that is effective in an animal model of mania. This case report describes a patient with treatment-resistant rapid cycling bipolar disorder who failed 15 psychotropics, individually or in various combinations (maximum of 6), but ultimately...
responded to levetiracetam monotherapy and remained without bipolar features during 1 year of maintenance treatment, excluding 1 week during which the patient was medication noncompliant. Further, methylphenidate used to treat comorbid attention deficit disorder did not precipitate manic features. **Conclusion:** Levetiracetam should be further studied for its potential use in the treatment of bipolar disorders.

**BD & Newer Anticonvulsants**

* Newer anticonvulsants in the treatment of bipolar disorder.

**Authors:** Yatham LN. - Division of Mood Disorders, University of British Columbia, Vancouver, British Columbia, Canada. yatham@interchange.ubc.ca

**Source:** J Clin Psychiatry. 2004;65 Suppl 10:28-35. Related Articles, Links

**Summary:** The anticonvulsants valproate and carbamazepine have efficacy in treating acute mania, but their efficacy in treating acute bipolar depression and preventing mood episodes remains uncertain. Despite this, and given their utility and widespread use, both are widely accepted as standard treatments for bipolar disorder. All the newer anticonvulsants that have become available during the last decade have been or are being assessed to determine their efficacy in the treatment of various phases of bipolar disorder. Among the newer anticonvulsants, some appear to have efficacy in treating core bipolar symptoms, while others have efficacy in treating psychiatric comorbidity such as substance abuse or an anxiety disorder. Lamotrigine is the most widely studied and is effective in treating and preventing bipolar depression, and it is the only anticonvulsant approved by the U.S. Food and Drug Administration as a maintenance treatment for bipolar disorder. Other newer anticonvulsants, levetiracetam, oxcarbazepine, phenytoin, and zonisamide offer promise, but further studies are required before they can be recommended for routine use to treat bipolar disorder. Gabapentin and topiramate do not appear to have efficacy in treating acute mania, but their utility in bipolar depression and prevention of mood episodes has not been studied in double-blind trials. Pregabalin has utility in treating generalized anxiety disorder, but it has not been studied in bipolar disorder. Given the success of lamotrigine in treating bipolar disorder, further double-blind controlled trials of the newer anticonvulsants in treating bipolar disorder are warranted. **Conclusion:** This article summarizes current evidence from trials of anticonvulsants in bipolar disorder and makes recommendations for their clinical use.

**BD & Levetiracetam**

* APA: Levetiracetam Appears Useful in Women and Children With Bipolar Disease

**Authors:** By Ed Susman - mgitlin@mednet.ucla.edu

**Source:** NEW YORK, NY -- May 10, 2004

**Summary:** The antiepileptic medication levetiracetam appears to offer relief of symptoms from bipolar disorder and other aggressive disorders with few adverse side effects, said researchers on May 4th there at the American Psychiatric Association Annual Meeting. Levetiracetam demonstrated that it could control symptoms in people with oppositional defiant disorder, intermittent explosive disorder, impulse-control disorder, and conduct disorder, as well as bipolar disorder.

"We are very excited about the use of this drug," said study coauthor Daniel Deutschman, MD, chief of psychiatry, Southwest General Health Center, Middleburg Heights, Ohio, and assistant clinical professor of psychiatry, Case Western Reserve University, Cleveland, Ohio.

"Treatment of bipolar and aggressive disorders can be challenging in terms of both controlling symptoms and managing medication side effects," Dr. Deutschman said. "We have been looking for a better method of stabilizing anger among patients -- conditions that can erupt into road rage and other problematic situations. We have been looking at other antiepileptics, but some previous compounds have proven to [either] have too many adverse side effects or to not be effective." With levetiracetam, the researchers said they have found a medication that, in their open-label studies, proved to offer symptom control with limited side effects (somnolence being the major one). "We were able to convince patients that levetiracetam would be simpler to take," Dr. Deutschman noted, adding that the need to draw blood from patients to check medication levels was a drawback with certain drugs -- especially when those drugs were administered to children. In the study involving aggressive disorders, Dr. Deutschman said about 45% of the 54 patients were able to control their symptoms with levetiracetam. Sixty-two percent of patients had oppositional defiant disorder. Dr. Deutschman said 11% of the patients stopped taking the medication because it didn’t seem to

**APA: Antiepileptic Levetiracetam Safe, Effective for Treating Bipolar or Aggressive Disorders**

**Authors:** By Bruce Sylvester

**Source:** NEW YORK, NY -- May 5, 2004

**Summary:** The antiepileptic medication levetiracetam appears to offer relief of symptoms from bipolar disorder and other aggressive disorders with few adverse side effects, said researchers on May 4th there at the American Psychiatric Association Annual Meeting. Levetiracetam demonstrated that it could control symptoms in people with oppositional defiant disorder, intermittent explosive disorder, impulse-control disorder, and conduct disorder, as well as bipolar disorder.

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be effective; 12% were unable to handle side effects. In the bipolar-disorders study, Dr. Deutschman and colleagues reported that 48.6% of the 109 patients achieved symptom control, which when compared with baseline, represented a statistically significant improvement. “We were surprised that the difference was such a robust P <.001,” Dr. Deutschman noted.

“The fact that we found such a strong and consistent response to lamotrigine despite the diversity of patients in these studies is extremely encouraging,” said lead author Douglas Deutschman, PhD, associate professor of biology, San Diego State University, San Diego, California, and son of the study's coauthor. The studies were investigator initiated, the senior Dr. Deutschman said, “But once UCB Pharma learned of the data we collected, the company awarded us unrestricted grants to complete the work.”

**Atypical BD Forme & New Anticonvulsants**

- **Relevance of new and newly rediscovered anticonvulsants for atypical forms of bipolar disorder.**

  **Authors:** Grunze H, Walden J. - Department of Psychiatry, LMU, Nussbaumstr. 7, D-80336 Munich, Germany. grunze@psy.med.uni-muenchen.de

  **Source:** J Affect Disord. 2002 Dec;72 Suppl 1:S15-21. Related Articles, Links

  **Summary:** The so-called atypical forms of bipolar disorder are not a rarity, but instead are rather the rule. Particularly in specialized settings such as the bipolar disorder clinic, the majority of patients are characterized by atypical manifestations (). Mixed states, psychotic mania and a rapid cycling course of bipolar disorder are a challenge both to pharmacological and non-pharmacological treatment. The benefit of classical mood stabilizers such as lithium and carbamazepine is limited in monotherapy, although valproate has a broader spectrum of activity in atypical bipolar disorders and is often used in combination with other agents. Thus, new treatment alternatives are needed urgently for optimizing the treatment of atypical bipolar disorder. During the last decade, several new antiepileptic drugs have been released, e.g. lamotrigine, gabapentin, tiagabine, topiramate and levetiracetam. Others have been available for some time, but only recently have become the focus of bipolar disorder research; for example, phenytoin, and especially, oxcarbazepine. Conclusion: This review will consider our current knowledge of the benefit of these new and newly rediscovered anticonvulsants in treating bipolar disorders, with a special focus on their value in treating atypical manifestations.

**Lamotrigine & Rapid Cycling BD II**

- **Lamotrigine therapy in treatment-resistant menstrually-related rapid cycling bipolar disorder: A case report.**

  **Authors:** Becker OV, Rasgon NL, Marsh WK, Glenn T, Ketter TA. - Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5723, USA.

  **Source:** Bipolar Disord. 2004 Oct;6(5):435-9. Related Articles, Links

  **Summary:** AIMS/OBJECTIVES: To evaluate lamotrigine in a woman with a 30-year history of treatment-resistant menstrually-entrained rapid cycling bipolar II disorder with follicular phase depressive and luteal phase mood elevation symptoms. METHODS: Lamotrigine was started at 5 mg/day and gradually increased up to 300 mg/day, while venlafaxine was tapered gradually and discontinued, and divalproex sodium 500 mg/day and levothyroxine 175 mcgm/day were continued. Daily self-reported mood ratings were obtained from the patient, using ChronoRecord software. RESULTS: As lamotrigine was increased gradually, mood cycle amplitude attenuated. There was notable decrease in the severity and duration of depressive symptoms specifically during the follicular phase of the menstrual cycle. At the time of submission of this paper, the subject had remained euthymic for a total of 12 months. Conclusion: This case suggests the potential utility of lamotrigine in treatment-resistant menstrually-related rapid cycling bipolar disorder, and raises the possibility that lamotrigine might be able to treat pathological entrainment of mood with the menstrual cycle. Both of these issues merit systematic assessment.

**BD & Quetiapine**

- **Quetiapine in bipolar disorder: Increasing evidence of efficacy and tolerability.**

  **Authors:** Cole P, Rabasseda X. - Medical Information Department, Prous Science, Provenca 388, Barcelona 08025, Spain

  **Source:** Drugs Today (Barc). 2004 Oct;40(10):837-52. Related Articles, Links

  **Summary:** Quetiapine is an atypical antipsychotic agent that has been approved for the treatment of schizophrenia in over 75 countries; it has been used to treat more than 4 million individuals since its launch in 1997. After quetiapine was found to improve mood and reduce aggression in patients with schizophrenia, researchers began investigating the drug in other indications. Of particular note is the incidence of extrapyramidal symptoms at levels similar to those seen with placebo. A phase III trial program in bipolar disorder is presently ongoing and includes five randomized, double-blind, controlled trials already reported and several other studies which are ongoing or planned. Conclusion: Quetiapine, as monotherapy or combined with mood stabilizers, significantly reduces measures of disease severity and acute mania in a variety of bipolar disorder patients, and displays excellent tolerability for a drug in its class.

**MDD prevention & Fluoxetine**

- **Fluoxetine treatment for prevention of relapse of depression in children and adolescents: A double-blind, placebo-controlled study.**

  **Authors:** Emslie GJ, Heiligenstein JH, Hoog SL, Wagner KD, Finding RL, McCracken JT, Nilsson ME, Jacobson JS. - University of Texas Southwestern Medical Center at Dallas, Texas, USA

  **Source:** Related Articles, Links

  **Summary:** OBJECTIVE: To compare fluoxetine 20 to 60 mg/day with placebo for prevention of relapse of major depressive disorder in children and adolescents who had achieved
Conclusions: During treatment with fluoxetine, children with BPD experience high levels of morbidity, typically respond unsatisfactorily to available treatments, and, so, require additional studies of novel treatments. We report on the first controlled study comparing acute and continuous clinical outcomes in RC and non-RC manic patients treated with olanzapine. Method: We analyzed data pooled from 2 placebo-controlled, double-blind, 3-to-4-week trials of olanzapine in mania (N = 254), 1 with an open-label extension up to 1 year (N = 113) and controlled supplementation with lithium or fluoxetine as needed, to compare demographic, clinical, and outcome measures between RC and non-RC subgroups of 254 DSM-IV manic patients. Results: RC (N = 90, 35%) versus non-RC patients (N = 164, 65%) were younger at intake (p = 0.2), less often psychotic (p < 0.001), and more likely to have familial bipolar disorder (p < 0.001), abused substances (p = 0.01), more previous hospitalizations (p = 0.04), and many more illness episodes (p < 0.01). In initial blinded trial outcomes, relative responses (> or = 50% improvement of mania) to olanzapine/placebo were similar in RC and non-RC subjects, though early responses to olanzapine favored RC over non-RC subjects (p = 0.03), and long-term outcomes favored non-RC subjects (p = 0.05). Fewer RC subjects achieved strictly defined initial symptomatic remission (p = 0.014) within a year; RC subjects were more likely to experience recurrences (p = 0.002), especially of depressive illness (< 0.001), and had more rehospitalizations (p = 0.01) and suicide attempts (p = 0.03). Conclusion: RC bipolar I patients showed major initial differences and more rapid initial clinical changes, especially toward depression, with less favorable long-term outcomes than non-RC cases during treatment with olanzapine. Inclusion of RC bipolar disorder patients can complicate therapeutic trials, but these patients require further study with additional responsive treatments to improve outcomes in RC bipolar disorder patients.
on therapy (250 mg or lower). Retrospectively abstracted clinical data identified nine patients with bipolar I disorder, as defined by DSMIV criteria, treated with low-dose clozapine at inpatient and outpatient settings. Monthly symptom evaluations were collected prospectively using standard assessments. Symptoms of mania and mood lability improved in all patients. Three patients demonstrated striking mood stabilization and returned to previous levels of functioning; five patients evidenced moderate improvement in mood stabilization and functioning; and one patient showed a minimal response. Overall, clozapine did not have a significant antidepressant effect. The mean clozapine dose at the end of the study was 156.3 +/- 77.6 mg/day, and duration of treatment was 12 months. Conclusion: Residual side effects were mild. The symptomatic improvement in these prospectively evaluated patients is consistent with our clinical impression in the majority of patients with bipolar disorder taking clozapine.

PPD

PPD & Discontinuation syndrome —

Postpartum depression recurrence versus discontinuation syndrome: observations from a randomized controlled trial.

Authors: Sunder KR, Wisner KL, Hanusa BH, Perel JM. - Department of Psychiatry, and Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA


Summary: OBJECTIVE: To differentiate characteristics of a discontinuation syndrome from a recurrence of major depressive disorder in the context of a randomized trial. METHOD: We performed a randomized clinical trial to compare the efficacy of sertraline versus placebo for the prevention of recurrent postpartum DSM-IV major depressive disorder. Women whose depression did not recur in the initial 17-week active treatment trial were followed through the taper phase (weeks 18-20). At week 17, 3 women assigned to placebo and 8 assigned to sertraline remained in the trial. Nine symptoms that characterize discontinuation syndrome were extracted from the 25-item Asberg Rating Scale for Side Effects (ASE) and assessed weekly during the taper phase. The 21-item Hamilton Rating Scale for Depression was used to evaluate depressive symptoms. RESULTS: In the taper phase, there were no significant differences between the sertraline- and placebo-treated women on the sum of the ASE-derived symptoms. Both groups had low levels of symptoms on the ASE during the weeks of taper. None of the 3 women assigned to placebo and 2 of the 8 women assigned to sertraline suffered a depressive recurrence within 6 weeks of the end of the study. Conclusion: A gradual taper of sertraline (75 mg) over 3 weeks did not lead to discontinuation syndrome; however, the systematic dissection of symptoms resulted in our conclusion that the duration of preventive therapy should be extended to 26 weeks (about 6 months) in subsequent randomized trials, consistent with the treatment guidelines for a single episode of depression.

The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial.

Authors: Misri S, Reebye P, Corral M, Mills L. - Department of, Faculty of Medicine, University of British Columbia and Reproductive Mental Health Programs, St. Paul's Hospital, Vancouver, British Columbia, Canada.

Source: J Clin Psychiatry. 2004 Sep;65(9):1236-41. Related Articles, Links

Summary: BACKGROUND: Approximately 10% to 16% of women experience a major depressive episode after childbirth. A significant proportion of these women also suffer from comorbid anxiety disorders. The purpose of this study was to evaluate whether the addition of cognitive-behavioral therapy (CBT) to standard antidepressant therapy offers additional benefits in the treatment of post-partum depression with comorbid anxiety disorders. METHOD: Thirty-five women referred to a tertiary care hospital outpatient program with a DSM-IV diagnosis of postpartum depression with comorbid anxiety disorder were randomly assigned to 1 of 2 treatment groups-paroxetine-only monotherapy group (N = 16) or paroxetine plus 12 sessions of CBT combination therapy group (N = 19)-for a 12-week trial. Progress was monitored by a psychiatrist blinded to treatment group, using the Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, Yale-Brown Obsessive Compulsive Scale, Clinical Global Impressions scale, and Edinburgh Postnatal Depression Scale. Data were analyzed using 2-tailed statistical tests at an alpha level of.05. The study was conducted from April 1, 2002, to June 30, 2003. RESULTS: Both treatment groups showed a highly significant improvement (p <.01) in mood and anxiety symptoms. Groups did not differ significantly in week of recovery, dose of paroxetine at remission, or measures of depression, anxiety, and obsessive-compulsive symptoms at outcome. Conclusion: Antidepressant monotherapy and combination therapy with antidepressants and CBT were both efficacious in reducing depression and anxiety symptoms. However, in this sample of acutely depressed/anxious postpartum women, there were no additional benefits from combining the 2 treatment modalities. Further research into the efficacy of combination therapy in the treatment of moderate-to-severe depression with comorbid disorders in postpartum women is recommended.

Schizophrenie

Instrument for detection of delirium in general hospitals: adaptation of the confusion assessment method.

Authors: Gonzalez M, de Pablo J, Fuente E, Valdes M, Peri JM, Nomdedeu M, Matrai S. - IDIBAPS Clinical Institute of Psychiatry and Psychology, Internal Medicine Department, Hospital Clinic, University of Barcelona, Spain.

Source: Psychosomatics. 2004 Sep-Oct;45(5):426-31

Summary: Delirium is a common and severe disorder that is often misdiagnosed. The use of screening instruments is advisable for its early detection and treatment. In this study, the authors present an adaptation of the Confusion Assessment Method.
Method in order to improve its psychometric properties. One hundred fifty-three elderly inpatients were assessed in a four-phase procedure. Interrater reliability was high (kappa = 0.89). Sensitivity was 90%, and specificity was 100%; the value for negative predictive accuracy was 97%, and the value for positive predictive accuracy was 100%. The adaptation has converged agreement with two other mental status tests, the Mini-Mental Status Examination and the Delirium Rating Scale. Our results suggest that the adaptation of the Confusion Assessment Method is sensitive, specific, reliable, and easy to use by clinicians.

Transcranial Magnetic Stimulation

Applications of Transcranial Magnetic Stimulation to Therapy in Psychiatry

by Antonio Mantovani, M.D., Ph.D., and Sarah H. Lisanby, M.D.

Source: Psychiatric Times August 2004 Vol. XXI Issue 9

Summary: Transcranial magnetic stimulation (TMS) is a non-invasive means of stimulating focal regions of the brain using magnetic fields. Since its introduction in 1985, TMS has been used to study localisation of brain functions, connectivity of brain regions and pathophysiology of neuropsychiatric disorders. The potential uses of TMS to treat psychiatric disorders are under active study. This article reviews the state of knowledge about the therapeutic potential of TMS in psychiatry.

The TMS Process

Transcranial magnetic stimulation is an investigational medical procedure performed by placing an electromagnetic coil on the scalp (Figure). High-intensity current is rapidly turned on and off in the coil through the discharge of a capacitor. This produces a time-varying magnetic field that lasts for about 100 to 200 microseconds. The magnetic field strength is about 1.5 to 2 tesla (about the same intensity as the static magnetic field used in clinical magnetic resonance imaging) at the surface of the coil, but the strength of the magnetic field drops off exponentially with distance from the coil. The proximity of the brain to the time-varying magnetic field results in current flow in neural tissue and in membrane depolarization. Transcranial magnetic stimulation is experimental; it is not approved by the U.S. Food and Drug Administration for the treatment of any disorder.

A striking effect of TMS occurs when one places the coil on the scalp over the primary motor cortex. A single TMS pulse of sufficient intensity causes involuntary movement in the muscle represented by that region of cortex. Thus, a TMS pulse produces a powerful but brief magnetic field that passes through the skin, soft tissue and skull. This induces electrical current in the skin, soft tissue and skull. This induces electrical current in neurons, causing depolarization that then has behavioral effects. The minimum magnetic field intensity needed to produce motor movement is known as the individual motor threshold.

Repeated application of TMS pulses at regular intervals is called repetitive TMS (rTMS). The physiological effects of TMS depend upon the site and frequency of stimulation. If the stimulation occurs faster than once per second (1 Hz), it is referred to as fast rTMS and can result in excitatory physiologic changes. On the contrary, if the frequency is low, it is referred to as slow rTMS and can have an inhibitory effect on brain excitability.

High-frequency rTMS carries a risk of seizure. Guidelines exist to reduce this risk by appropriate screening of participants for seizure risk factors, titrating the individual motor threshold and limiting rTMS dosage (Belmaker et al., 2003; Wassermann, 1998). The ability to focaly alter cortical excitability opens up the potential to modulate cortical circuitry for potential therapeutic benefit. The focality of the effects also presents a challenge to clinical application, because it is necessary to know the circuitry of the underlying disorder to guide where and how to stimulate to ameliorate its symptoms.

Sex differences in brain function & SCZ

Sex differences in functional connectivity in first-episode and chronic schizophrenia patients.

Authors: Slewa-Younan S, Gordon E, Harris AW, Haig AR, Brown KJ, Flor-Henry P, Williams LM. - The Brain Dynamics Centre, Acacia House, Westmead Hospital, Westmead NSW, 2145, Australia. shameran@biru.wsuhs.nsw.gov.au

Source: Am J Psychiatry. 2004 Sep;161(9):1595-602

Summary: There has been consistent evidence for a lower incidence and milder course of schizophrenia in women, yet there have been very few investigations of sex differences in brain function in this disorder. This study used a new high-temporal-resolution measure of functional brain connectivity to test the prediction that female patients would show relatively greater inter- and intrahemispheric connectivity than male patients, particularly in the early stage of schizophrenia. METHOD: Forty patients with chronic schizophrenia (20 women and 20 men) and 24 patients with first-episode schizophrenia (12 women and 12 men) and their respective matched comparison groups completed a conventional auditory oddball task. Phase synchronous gamma (40 Hz) activity was extracted from EEG recording during the task and time-locked to the oddball (target) stimuli. RESULTS: Chronic schizophrenia subjects showed a reduction in global functional connectivity (lower gamma phase synchrony) relative to their matched healthy subjects. Unexpectedly, this reduction was most apparent in female patients. By contrast, while first-episode patients showed a general reduction in the speed of frontal connectivity, the speed of global connectivity was relatively faster in female patients.

Conclusions: This is the first study to investigate sex differences in schizophrenia that used the functional connectivity measure of gamma phase synchrony. The results suggest that in female patients with schizophrenia, additional breakdowns in brain network connectivity may develop with illness chronicity.

Temporal gyrus gray & SCZ

Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study.

Authors: Onitsuka T, Shenton ME, Salisbury DF, Dickey CC, Kasai K, Toner SK, Frumin M, Kikinis R, Jolesz FA, McCarley RW. - Department of Psychiatry (116A), Boston VA Healthcare System, Brockton Division, Harvard Medical School, 940 Belmont St., Brockton, MA 02301. robert.mccarley@hms.harvard.edu

Source: Am J Psychiatry. 2004 Sep;161(9):1603-11

Summary: OBJECTIVE: The middle temporal gyrus and inferior temporal gyrus subserve language and semantic memory processing, visual perception, and multimodal sensory integration. Functional deficits in these cognitive processes have been well documented in patients with schizophrenia. However, there have been few in vivo structural magnetic resonance imaging (MRI) studies of the middle temporal gyrus and inferior...
temporal gyrus in schizophrenia. METHOD: Middle temporal gyrus and inferior temporal gyrus gray matter volumes were measured in 23 male patients diagnosed with chronic schizophrenia and 28 healthy male subjects by using high-spatial-resolution MRI. For comparison, superior temporal gyrus and fusiform gyrus gray matter volumes were also measured. Correlations between these four regions and clinical symptoms were also investigated. RESULTS: Relative to healthy subjects, the patients with chronic schizophrenia showed gray matter volume reductions in the left middle temporal gyrus (13% difference) and bilateral inferior temporal gyrus (10% difference in both hemispheres). In addition, the patients showed gray matter volume reductions in the left superior temporal gyrus (13% difference) and bilateral fusiform gyrus (10% difference in both hemispheres). More severe hallucinations were significantly correlated with smaller left hemisphere volumes in the superior temporal gyrus and middle temporal gyrus. Conclusions: These results suggest that patients with schizophrenia evince reduced gray matter volume in the left middle temporal gyrus and bilateral reductions in the inferior temporal gyrus. In conjunction with findings of left superior temporal gyrus reduction and bilateral fusiform gyrus reductions, these data suggest that schizophrenia may be characterized by left hemisphere-selective dorsal pathophysiology and bilateral ventral pathophysiology in temporal lobe gray matter.

**Effects of a Functional COMT Polymorphism on Prefrontal Cognitive Function in Patients With 22q11.2 Deletion Syndrome.**

**Authors:** Bearden CE, Jawad AF, Lynch DR, Sokol S, Kanes SJ, McDonald-McGinn DM, Saitta SC, Harris SE, Moss E, Wang PP, Zackai E, Emanuel BS, Simon TJ. - UCLA Department of Psychiatry and Biobehavioral Sciences, 300 UCLA Medical Plaza, Room 2265, Los Angeles, CA 90095. cbearden@mednet.ucla.edu

**Source:** Am J Psychiatry. 2004 Sep;161(9):1700-2

**Summary:** OBJECTIVE: The 22q11.2 deletion syndrome (DiGeorge/velocardiofacial syndrome) is associated with attentional problems and executive dysfunction, and is one of the highest known risk factors for schizophrenia. These behavioral manifestations of 22q11.2 deletion syndrome could result from hapatolysinsufficiency of the catechol-O-methyltransferase (COMT) gene, located within the 22q11 region. The goal of the present study was to examine COMT genotype as a predictor of prefrontal cognitive function in patients with 22q11.2 deletion syndrome. METHOD: Patients with confirmed 22q11.2 deletions (N=44) underwent neurocognitive testing following Val(158)Met genotyping (Met hemizygous: N=16; Val hemizygous: N=28). RESULTS: Analyses of covariance revealed that Met-hemizygous patients performed significantly better on a composite measure of executive function (comprising set-shifting, verbal fluency, attention, and working memory) than did Val-hemizygous patients. Conclusions: These data are consistent with those of previous studies in normal individuals, suggesting that a functional genetic polymorphism in the 22q11 region may influence prefrontal cognition in individuals with COMT hapatolysinsufficiency.

**Cessation in a Patient With Schizophrenia After Treatment With Ziprasidone**

**Authors:** Vartian, Brian A BSc; Hawken, Emily R MSc; Delva, Nicholas J MD

**Source:** Addictive Disorders & Their Treatment. 3(3):138-143, September 2004

**Summary:** A patient suffering from schizophrenia stopped smoking 9 days after the initiation of treatment with ziprasidone and had not resumed smoking 2 years later. While a reduction in cigarette consumption has been previously observed after the switch from typical to atypical antipsychotics, spontaneous cessation of smoking has not been previously reported during treatment with ziprasidone. Cigarette smoking is very common in patients with schizophrenia, and it is a major cause of morbidity and mortality in this group. Any treatment that assists these patients to stop smoking is thus of great value. The relationships between schizophrenia, smoking, and antipsychotic medication are complex. In the context of a brief but comprehensive literature review, we discuss potential explanations for the successful outcome seen in our patient.

**SCZ & Amisulpride**

**Premenstrual Dysphoric Disorder: An Update [Record Supplied By Aries Systems]**

**Authors:** McKeage K, Plasker GL. - Adis International Limited, Auckland, New Zealand

**Source:** CNS Drugs. 2004;18(13):933-56. Related Articles, Links

**Summary:** Amisulpride (Solian), a substituted benzamide derivative, is a second-generation antipsychotic that preferentially binds to dopamine D2/D3 receptors in limbic rather than striatal structures. High dosages preferably antagonise postsynaptic D2/D3 receptors, resulting in reduced dopamine transmission, and low dosages preferably block presynaptic D2/D3 receptors, resulting in enhanced dopamine transmission. Amisulpride (200-1200 mg/day) was at least as effective as haloperidol and as effective as risperidone or olanzapine, in studies of up to 1 year in patients with schizophrenia manifesting predominantly positive symptoms. Amisulpride (50-300 mg/day) was significantly more effective than placebo in studies of up to 6 months in patients manifesting predominantly negative symptoms. Quality of life was also improved significantly more in patients receiving amisulpride than in those receiving haloperidol in 4- and 12-month studies in patients with predominantly mixed symptoms. Amisulpride was generally well tolerated in clinical trials. In patients with predominantly positive symptoms, amisulpride appeared to be better tolerated than haloperidol and was tolerated as well as risperidone and olanzapine. The incidence of extrapyramidal adverse effects with amisulpride was lower than with haloperidol but was generally similar to risperidone or olanzapine. Weight gain with amisulpride was less than that with risperidone or olanzapine and, unlike these agents, amisulpride does not seem to be associated with diabetogenic effects. Plasma prolactin levels are increased during amisulpride therapy and amenorrhoea occurs in about 4% of women. The incidence of adverse events with low dosages of amisulpride (< or = 300 mg/day) in patients with predominantly negative symptoms was similar to that observed with placebo. In conclusion, oral amisulpride (200-1200 mg/day) is at least as effective as haloperidol, and as effective as risperidone or olanzapine, in the treatment of patients with schizophrenia.
schizophrenia manifesting predominantly positive symptoms. In the treatment of patients manifesting predominantly negative symptoms, low dosages of amisulpride (50-300 mg/day) are significantly more effective than placebo. Amisulpride appears to be better tolerated than haloperidol, causing a lower incidence of extrapyramidal adverse effects and an improved quality of life. Compared with risperidone or olanzapine, amisulpride is more likely to cause hyperprolactinaemia, but has a lower propensity to cause weight gain and does not seem to be associated with diabetogenic effects. Conclusion: Thus, amisulpride is an effective and well tolerated option for the first-line treatment of patients with acute schizophrenia as well as for those requiring long-term maintenance therapy.

SCZ, ECT & Clozapine

Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia

Authors: Kho KH, Blansjaar BA, de Vries S, Babuska D, Zwinderman AH, Linszen DH. - GGZ Delfland, St Jorisweg 2, 2612, GA Delft, The Netherlands


Summary: OBJECTIVE. This open label study describes the efficacy of electroconvulsive therapy (ECT) as adjunctive treatment in clozapine nonresponders suffering from schizophrenia. METHOD. The results of clozapine and ECT treatment in 11 clozapine nonresponders suffering from schizophrenia are reported in terms of remission and relapse. RESULTS. Eight patients had a remission with this combination treatment. After remission of symptoms five patients had a relapse. Three of the five patients who relapsed had a second successful ECT course and remained well with maintenance ECT and clozapine. No evidence for adverse effects was found. Conclusion: Adjunctive ECT can be efficacious in clozapine nonresponders suffering from schizophrenia.

PMS & PMDD

PMDD ; Current Information

PMDD : Brief review of current information

Authors: Freeman EW; Sondheimer SJ - Department of Obstetrics/Gynecology and the Psychiatry, University of Pennsylvania School of Medicine, Philadelphia.


Summary: Premenstrual dysphoric disorder (PMDD) represents the more severe and disabling end of the spectrum of premenstrual syndrome and occurs in an estimated 2% to 9% of menstruating women. The most frequent PMDD symptoms among women seeking treatment consist of anger/irritability, anxiety/tension, feeling tired or lethargic, mood swings, feeling sad or depressed, and increased interpersonal conflicts. Women who develop PMDD appear to have serotonergic dysregulation that may be triggered by cyclic changes in gonadal steroids. The marked increase in the number of well-designed placebo-controlled studies in the past decade has established several selective serotonin reuptake-inhibiting antidepressants as effective first-line treatments for this disorder. Both continuous dosing and intermittent luteal dosing strategies lead to rapid improvement in symptoms and functioning. The present article provides a brief review of current information on the epidemiology, clinical presentation, neurobiology, and treatment of PMDD.

PMDD & MDD

Premenstrual dysphoric disorder and risk for major depressive disorder: a preliminary study.

Authors: Hartlage SA; Arduino KE; Gehlert S - Rush-Presbyterian-St. Luke’s Medical Center and Rush Medical College, Chicago, IL 60612-3864, USA

Source: J Clin Psychol 2001 Dec;57(12):1571-8 (ISSN: 0021-9762)

Summary: Investigators examined whether premenstrual dysphoric disorder (PMDD) poses a risk for major depressive disorder (MDD). In an initial study, women rated premenstrual symptoms and functional impairment daily for two menstrual cycles. A semi-structured diagnostic interview was given to obtain psychiatric histories and differentiate PMDD from premenstrual exacerbations of other disorders. Participants in this pilot study were eight women with PMDD and a random subgroup without PMDD (n = 9) initially. Another semi-structured interview was given to diagnose psychiatric disorders occurring during a two-year follow-up interval. In all, seven of the eight women with PMDD developed MDD within two years, including all those who had never had MDD before. Conclusion: The odds that a woman with PMDD developed MDD were 14 times
the odds that a woman without PMDD developed MDD (p < .05). Premenstrual dysphoric disorder may be a prodrome of or cause risk factor for MDD. Preliminary evidence for the diagnostic validity of PMDD is provided.

**PMDD & Dysmenorrhea Dietary habits**

- **Premenstrual syndrome and associated symptoms in adolescent girls (In Process Citation)**

  **Authors**: Deman O; Kanbur NO; Tokur TE; Kutluk T - Section of Adolescent Medicine, Department of Pediatrics, Ihsan Dogramaci Childrens Hospital, Hacettepe University School of Medicine, 06100 Ankara, Turkey


  **Summary**: Objective: To investigate the frequency of premenstrual syndrome (PMS) associated symptoms and effects of nutrition on PMS in adolescent girls. Patients and methods: One hundred and seventy-one adolescent girls who had menstrual cycles were included in this study. They were given a questionnaire on criteria for PMS, dysmenorrhea and regularity of menstrual cycle. Modified Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria were used for the diagnosis of PMS. We also investigated which nutritional supplements affect the PMS-associated symptoms and signs. Results: One hundred and five adolescent girls out of 171 (61.4%) met DSM-IV criteria for PMS. There was an association between dysmenorrhea and PMS in 60 (57.1%). Half of the girls, i.e. 52 (49.5%) had mild, 39 (37.1%) had moderate and 14 (13.4%) had severe PMS. The most common symptom of PMS was negative affect particularly in the form of stress (87.6%) and nervousness (87.6%). There was a statistically significant negative relationship between milk consumption and the symptoms of PMS. Conclusion: PMS and dysmenorrhea are frequently overlapping. We also found that PMS is associated with dietary habits.

**PMS & Complementary therapy**

- **Effects of qi therapy (external qigong ) on premenstrual syndrome: a randomized placebo-controlled study (In Process Citation)**

  **Authors**: Jang HS; Lee MS - Department of Nursing, Wonkwang Health Science College, Iksan, Korea


  **Summary**: OBJECTIVES: To assess the effects of qi therapy on premenstrual symptoms in women with premenstrual syndrome (PMS). DESIGN: A randomized placebo-controlled trial. SUBJECTS: Thirty-six (36) college women with symptoms of PMS.INTERVENTION: After 2 months of screening, subjects with PMS were randomized to receive real qi therapy (18 subjects) or placebo (18 subjects). The subjects were informed that they would receive one of two types of treatment. They did not know which treatment they received. Each intervention was performed eight times during the second and third cycles with subjects completing a PMS diary Results: There were significant improvements in the symptoms of negative feeling, pain, water retention, and total PMS symptoms in subjects receiving qi therapy compared to placebo controls. Conclusion: Qi therapy may be an effective complementary therapy for managing the symptoms of PMS.

**PMDD, PMS & Suicide**

- **Premenstrual symptoms and luteal suicide attempts (In Process Citation)**

  **Authors**: Baca-Garcia E; Diaz-Sastre C; Ceverino A; Garcia Resa E; Oquendo MA; Saiz-Ruiz J; De Leon J - Department of Psychiatry, Fundacion Jimenez Diaz, Madrid, Spain


  **Summary**: OBJECTIVE: If premenstrual symptoms (PMS) are temporally and specifically associated with suicidal attempts, suicide attempts in women with PMS should occur more frequently in the luteal phase. METHOD: In a general hospital, 125 fertile female suicide attempters (and 83 blood donors as controls) with regular menstrual cycles were prospectively studied. A retrospective DSM-IV diagnosis of Premenstrual Dysphoric Disorder (PMDD) was made. RESULTS: Attempts during the luteal phase were not more frequent in females with PMDD (34%, 23/68) than in those without PMDD (35%, 20/57). The sample had enough power to detect medium and large effect sizes. As expected, there was a significantly higher frequency of PMDD in suicide attempters than in the controls (54% vs 6%; Fisher's exact test, p <= 0.001). Conclusion: This study was limited by the use of retrospective PMDD diagnosis but suggests that PMDD may not be associated with suicidal acts during the luteal phase, when PMS are present.

**PMDD, Hormones & Psychotropic drug**

- **Current update of hormonal and psychotropic drug treatment of premenstrual dysphoric disorder**

  **Authors**: Freeman EW - Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, 3400 Spruce Street, 2 Dulles, Mudd Suite, Philadelphia, PA 19104, USA; freemane@mail.med.upenn.edu

  **Source**: Curr Psychiatry Rep 2002 Dec;4(6):435-40  (ISSN: 1523-3812)

  **Summary**: This review discusses the current status of diagnosis and treatment of premenstrual dysphoric disorder (PMDD), with an emphasis on studies that have been published in the medical literature during the 2001 to 2002 interval. Serotonergic antidepressants are effective for PMDD, and are currently considered the first-line treatment. Recent clinical trials have shown that selective serotonin reuptake inhibitors, taken only during the symptomatic luteal phase, are also effective for PMDD. One study reported efficacy for a slow-release formulation of fluoxetine that was taken two times during the menstrual cycle. Oral contraceptives still lack definitive evidence of efficacy as a treatment for PMDD, although a new contraceptive formulation has appeared promising for the mood and behavioral symptoms of the disorder. Conclusion: The results of a meta-analysis of the published trials of progestrone and progestins further indicate that these hormones are not effective in the management of PMDD.

**PMS, PMDD, Life Style & SSRI**

- **Premenstrual syndrome and premenstrual dysphoric disorder**

  **Authors**: Eberly SD; Freitas AS - Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, 3400 Spruce Street, 2 Dulles, Mudd Suite, Philadelphia, PA 19104, USA; freemane@mail.med.upenn.edu

  **Summary**: This review discusses the current status of diagnosis and treatment of premenstrual dysphoric disorder (PMDD), with an emphasis on studies that have been published in the medical literature during the 2001 to 2002 interval. Serotonergic antidepressants are effective for PMDD, and are currently considered the first-line treatment. Recent clinical trials have shown that selective serotonin reuptake inhibitors, taken only during the symptomatic luteal phase, are also effective for PMDD. One study reported efficacy for a slow-release formulation of fluoxetine that was taken two times during the menstrual cycle. Oral contraceptives still lack definitive evidence of efficacy as a treatment for PMDD, although a new contraceptive formulation has appeared promising for the mood and behavioral symptoms of the disorder. Conclusion: The results of a meta-analysis of the published trials of progestrone and progestins further indicate that these hormones are not effective in the management of PMDD.
GUIDELINES FOR MANAGEMENT (RECORD SUPPLIED BY PUBLISHER)

Authors: Steiner M - Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ont. mst@hs.mcmaster.ca.


Summary: The inclusion of research diagnostic criteria for premenstrual dysphoric disorder (PMDD) in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, recognizes the fact that some women have extremely distressing emotional and behavioural symptoms premenstrually. PMDD can be differentiated from premenstrual syndrome (PMS), which presents with milder physical symptoms, headache, and more minor mood changes. In addition, PMDD can be differentiated from premenstrual magnification of physical or psychological symptoms of a concurrent psychiatric or medical disorder. As many as 75% of women with regular menstrual cycles experience some symptoms of PMS, according to epidemiologic surveys. PMDD is much less common; it affects only 3% to 8% of women in this group. The etiology of PMDD is largely unknown, but the current consensus is that normal ovarian function (rather than hormone imbalance) is the cyclical trigger for PMDD-related biochemical events within the central nervous system and other target organs. The serotonergic system is in a close reciprocal relation with the gonadal hormones and has been identified as the most plausible target for interventions. Thus, beyond conservative treatment options such as lifestyle and stress management, other non-antidepressant treatments, or the more extreme intervielements that eliminate ovulation altogether, selective serotonin reuptake inhibitors (SSRIs) are emerging as the most effective treatment option. Conclusion: Results from several randomized, placebo-controlled trials in women with PMDD have clearly demonstrated that SSRIs have excellent efficacy and minimal side effects. More recently, several preliminary studies indicate that intermittent (premenstrual only) treatment with selective SSRIs is equally effective in these women and, thus, may offer an attractive treatment option for a disorder that is itself intermittent.

PMDD & Venlafaxine

Efficacy and tolerability of premenstrual use of venlafaxine (flexible dose) in the treatment of premenstrual dysphoric disorder.

Authors: Cohen LS, Soares CN, Lyster A, Cassano P, Brandes M, Leblanc GA. - Perinatal and Reproductive Psychiatry Clinical Research Program, Massachusetts General Hospital (MGH), Harvard Medical School, Boston, MA 02114, USA. LCOHEN2@PARTNERS.ORG


Summary: The objective of this study was to examine the efficacy and tolerability of intermittent dosing of venlafaxine for the treatment of premenstrual dysphoric disorder. One hundred and twenty-four women aged 18 to 45 years, with regular menstrual cycles and who reported significant premenstrual symptoms, were assessed prospectively to confirm their diagnosis of premenstrual dysphoric disorder. Twenty subjects with confirmed premenstrual dysphoric disorder entered a single-blind, placebo phase (1 cycle). Placebo nonresponders (n = 12) received 2 cycles of intermittent (premenstrual) treatment with venlafaxine (75 to 112.5 mg/d). Subjects initiated treatment 14 days before the anticipated onset of menses and discontinued it on the second day of bleeding. Doses could be adjusted after cycle 1 based on subjects’ response and tolerability. Response to treatment was assessed based on changes in the Daily Rating Severity of Problems and Premenstrual Tension Syndrome Questionnaire scores from baseline (before the placebo cycle), as well as Clinical Global Impression-Severity scores. Discontinuation symptoms were assessed between treatment cycles, using the Discontinuation-Emergent Signs and Symptoms questionnaire. Eleven subjects concluded 2 cycles of intermittent dosing with venlafaxine. Nine subjects (81.8%) showed satisfactory response based on Clinical Global Impression of < or = 2. Changes in Daily Rating Severity of Problems scores and subscores (depression, physical symptoms, and anger) and in Premenstrual Tension Syndrome Questionnaire scores were significant (P < 0.05 for all comparisons; Wilcoxon tests). Conclusion: Intermittent treatment was well tolerated. This preliminary report suggests that premenstrual use of venlafaxine is an efficacious and well-tolerated treatment for premenstrual dysphoric disorder.

AMT, VLF & Prophylactic Migraine

Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study.

Authors: Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. - Department of Neurology, Faculty of Medicine, Firat University, TR 23119 Elazig, Turkey


Summary: In patients with migraine with or without aura the prophylactic effect of amitriptyline (AMT) and venlafaxine (VLF) was compared in a randomized double-blind crossover study. Intolerable side effects resulted in drop out of five patients on AMT (due to hypersomnia, difficulty in concentration and orthostatic hypotension) and one patient on VLF (because of nausea and vomiting). Following the run-in period the patients (Formula: see text) were randomly treated with one of the study medications for 12 weeks. After a wash-out period lasting 4 weeks the patients were treated with the other drug for further 12 weeks. Conclusion: Both drugs had significant beneficial effect on pain parameters. Total number of side effects of VLF was low when compared with the side effect profile of AMT. In conclusion, it is suggested that VLF may be considered for the prophylaxis of migraine because of its low and/or tolerable side effect properties.

SSRIs & Negative Symptoms

Selective serotonin re-uptake inhibitor augmentation in the treatment of negative symptoms of schizophrenia.

Authors: Silver H. - Sha’ar Menashe Mental Health Center, Mobile Post Hefer 38814, Israel. mdsilver@tx.technion.ac.il


Summary: Negative symptoms are core features of schizophrenia that respond poorly to first-generation psychotropes.
antipsychotics and present a major obstacle in rehabilitation. Patients may be somewhat more responsive to clozapine and second-generation antipsychotics but even then, considerable impairment remains. This paper reviews the use of selective serotonin re-uptake inhibitor (SSRI) augmentation of antipsychotics in the treatment of negative symptoms in schizophrenia. Important methodological issues particular to the study of negative symptoms are also discussed. Current evidence indicates that at least two SSRIs, fluvoxamine and fluoxetine, can ameliorate primary negative symptoms in chronic schizophrenic patients treated with first-generation antipsychotics. Onset of improvement may be detected within 2 weeks of starting treatment. The combination is well-tolerated, although as antipsychotic drug concentrations may rise, close monitoring of drug doses and possibly drug concentrations is needed. So far, evidence regarding SSRI augmentation of second-generation antipsychotics is limited and in view of the increasing use of these newer agents, controlled studies are urgently needed. SSRI augmentation may be a useful addition to the treatment of schizophrenic patients with persistent negative symptoms. Conclusion: The paradoxical findings that both clozapine, a serotonin antagonist, and an SSRI antidepressant added to antipsychotics, can improve negative symptoms suggests that these pharmacologically distinct treatments may share common final mechanisms. A better understanding of these mechanisms can shed light on the pathogenesis of negative symptoms and provide new targets for drug development.

**Clozapine & Leukopenia**

Leukopenia in clozapine treated patients may be induced by other drugs: A case series.

**Authors**: Imbarlina MJ, Sarkar S, Marwah S, Parepally H, Johnston PR, Brar JS, Chengappa KN. - Special Studies Center at Mayview State Hospital.


Summary: The combination of clozapine and other potentially leukopenic drugs may pose a greater risk for neutropenia. However, neutropenia may not always be due to clozapine. When adding potentially leukopenic drugs, clinicians should look for possible alternatives especially as clozapine is often a drug used as the last resort in treatment refractory schizophrenia.

**Ziprasidone, Efficacy & Tolerance**

Ziprasidone: First Year Experience in a Hospital Setting.

**Authors**: Centorrino, Franca Md; Maclean, Elizabeth PharmD; Salvatore, Paola Md; Kidwell, Jennifer E.; Fogarty, Kate V.; Berry, Judith M. Ma; Baldessarini, Ross J. Md

**Source**: Journal of Psychiatric Practice. 10(6):364-6

Summary: Background: The antipsychotic drug ziprasidone, FDA-approved and introduced in the United States in February 2001 for the treatment of schizophrenia, appears to have similar efficacy but better tolerability than older antipsychotics and requires further evaluation under clinical conditions. Methods: We analyzed medical records of McLean Hospital inpatients treated with ziprasidone between March 2001 and February 2002, gathering data on DSM-IV diagnoses, presenting symptoms, dosing, concomitant psychotropic medications, clinical changes, adverse effects, and electrocardiographic (ECG) findings. Results: Ziprasidone was given to 151 inpatients (3.4% of admissions; 108 women, 43 men), aged 37.5 +/- 11.4 years, who presented with depression (n = 79), psychosis (n = 46), mania (n = 18), bipolar mixed-states (n = 4), or other conditions (n = 4). Daily doses averaged 49.8 +/- 34.1 mg initially and 83.2 +/- 46.3 mg at discharge; the greatest dose increases during hospitalization (by a mean of 61%) were in patients with schizoaffective disorder (n = 46; 30% of cases). In 41 cases (27%), ziprasidone was the only antipsychotic at discharge; in 61 (40%) it was used with other antipsychotics. Ziprasidone was discontinued during hospitalization in 49 cases (32.5%), due to lack of efficacy (n = 26; 17.2%), adverse effects (n = 13; 8.6%), or reasons not stated (n = 10, 6.6%). Of 70 patients for whom ECG data were obtained during treatment with ziprasidone, 8 (11%) had QTc intervals > 500 msec during treatment, but none of the 39 patients with ECGs both before and during ziprasidone treatment showed clinically meaningful increases in QTc intervals. Ziprasidone was discontinued in 4 patients (2.6%) due to concern about QTc intervals, but in no case was the QTc interval >= 500 msec or associated with clinical cardiac toxicity. Improvements in CGI and GAF scores from admission to discharge were similar across diagnoses and unrelated to length of stay or ziprasidone dose. Conclusion: Ziprasidone was well tolerated by hospitalized patients with various major psychiatric disorders and may be of value in conditions other than schizophrenia.

**Antidepressants, Migraine & CIB**

Therapy of primary headaches: the role of antidepressants.

**Authors**: Colombo B, Annovazzi PO, Comi G.- Department of Neurology, Scientific Institute, Ospedale San Raffaele Headache Research Unit, Via Olgettina 48, Milan, Italy. colombo.bruno@hsr.it


Summary: Antidepressants are included in evidence-based guidelines for the prophylactic therapy of migraine. Although they can cause several side effects depending on the neurochemical activity, and are to be used with caution in older patients, some of them have a well-documented efficacy. Amitriptyline is classified as a Group 1 drug, whereas Fluoxetine is included in Group 2. There is fair support for the effectiveness of other serotonin reuptake inhibitors in migraine prevention. Conclusion: Amitriptyline has demonstrated a consistent efficacy in Chronic Tension Type Headache, and Mirtazapine has a promising profile for the treatment of the same disease.

**Fluvoxamine & Multiple sclerosis**

Fluvoxamine treatment of major depression associated with multiple sclerosis.

**Authors**: Benedetti F, Campori E, Colombo C, Smeraldi E. - Department of Neuropsychiatric Sciences, Universita Vita-Salute San Raffaele, School of Medicine, Milan, Italy. benedetti.francesco@hsr.it

**Source**: J Neuropsychiatry Clin Neurosci. 2004 Summer; 16 (3): 364-6

Summary: Fluvoxamine 200 mg was administered for 3 months

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بحث حول موضوع الطب النفسي 5-1405 - د. ف. 105
to a group of 43 interferon beta-1b treated patients affected by major depression associated with multiple sclerosis. Despite a 16.3% attrition rate, 79% of patients achieved response. The drug was well tolerated.

CITALOPRAM & JAW TREMOR

| Authors: | Tarlaci S.- Ozel Ege Saglik Hastanesi, Alsancak, 35040 Bornova, Izmir, Turkey. |
| Source: | Clin Neurol Neurosurg. 2004 Dec;107(1):73-5. Related Articles, Links |
| Summary: | A variety of medications can induce or enhance a tremor. Tremors most commonly affect the limbs, especially the arms. We report a patient who presented with a 5-6Hz jaw tremor with a temporal association with the administration of citalopram. To our knowledge, this is the first report in literature, of a transient jaw tremor associated with citalopram. According to the current data. Conclusion: Citalopram-induced jaw tremor can be explained by an indirect inhibitory effect on central dopaminergic activity. |

ARIPIPRAZOLE & NMS

| Authors: | Chakraborty N, Johnston T. - Department of Psychiatry, Ailsa Hospital, Ayr, UK. nandini_dass@rediffmail.com |
| Summary: | Aripiprazole, an atypical antipsychotic with a novel method of action, has only recently been awarded a license in the UK. We report our first patient to receive this drug, who had treatment-resistant schizophrenia and developed neuroleptic malignant syndrome (NMS) with aripiprazole. To our knowledge, this is the first published case report involving aripiprazole and NMS in a potentially fatal medical emergency. Conclusion: Further experience with this drug should indicate whether this is an isolated case (as described with other atypical antipsychotics) or constitutes a more serious risk than that suggested by the relatively beneficial therapeutic profile described in the literature to date. |

SSRI RESPONSE & THYROID HORMONES

| Authors: | Michael Gitlin, MD; Lori L. Altshuler, MD; Mark A. Frye, MD; Rita Suri, MD; Emily L. Huynh, BA; Lynn Fairbanks, PhD; Michael Bauer, MD; Stanley Korenman, MD |
| Summary: | Objective: To examine the relation between baseline measurements of thyroid function and response to selective serotonin reuptake inhibitors (SSRIs) and to consider the effect of these antidepressants on thyroid hormone levels. Methods: Nineteen subjects with major depression, but without a history of thyroid treatment or lithium treatment, were treated openly with either sertraline or fluoxetine in a university-affiliated tertiary care hospital. Hamilton Depression Rating Scale (Ham-D) scores were measured before and after treatment. Clinical Global Impressions (CGI) scores were measured at study end. Thyroid data, consisting of values for thyroid-stimulating hormone (TSH), triiodothyronine (T3, measured by radioimmunoassay [RIA]), thyroxine (T4, measured by RIA) and free T4, were collected before and after treatment. Complete thyroid data were available for 17 subjects. Data were collected during 1997-1999. Results: Baseline TSH correlated strongly with response to treatment as measured by change in Ham-D scores (r = 0.64, p = 0.003). Low TSH values correlated with greater improvement in depressive symptoms. Thyroid hormone levels decreased with treatment, but these decreases did not correlate with clinical improvement. Conclusion: Baseline thyroid function, as measured by serum TSH, may predict a patient's response to antidepressant treatment with SSRIs. Optimal thyroid function, beyond simply being within the normal laboratory values, may be necessary for an optimal response to antidepressants. |

LEVETIRACETAM & PHARMACOKINETICS

| Authors: | Patsalos PN. - Pharmacology and Therapeutics Unit, Department of Clinical and Experimental Epilepsy, Institute of Neurology/The National Hospital for Neurology and Neurosurgery, London, UK. P.Patsalos@ion.ucl.ac.uk |
| Summary: | Since 1989, eight new antiepileptic drugs (AEDs) have been licensed for clinical use. Levetiracetam is the latest to be licensed and is used as adjunctive therapy for the treatment of adult patients with partial seizures. AEDs. Pharmacokinetic studies of levetiracetam have been conducted in healthy volunteers, in adults, children and elderly patients with epilepsy, and in patients with renal and hepatic impairment. After oral ingestion, levetiracetam is rapidly absorbed, with peak concentration occurring after 1.3 hours, and its bioavailability is >95%. Co-ingestion of food slows the rate but not the extent of absorption. Levetiracetam is not bound to plasma proteins and has a volume of distribution of 0.5-0.7 L/kg. Plasma concentrations increase in proportion to dose over the clinically relevant dose range (500-5000 mg) and there is no evidence of accumulation during multiple administration. Steady-state blood concentrations are achieved within 24-48 hours. The elimination half-life in adult volunteers, adults with epilepsy, children with epilepsy and elderly volunteers is 6-8, 6-8, 5-7 and 10-11 hours, respectively. Approximately 34% of a levetiracetam dose is metabolised and 66% is excreted in urine unmetabolised; however, the metabolism is not hepatic but occurs primarily in blood by hydrolysis. Autoinduction is not a feature. As clearance is renal in nature it is directly dependent on creatinine clearance. Consequently, dosage adjustments are necessary for patients with moderate to severe renal impairment. To date, no clinically relevant pharmacokinetic interactions between AEDs and levetiracetam have been identified. Similarly, levetiracetam does not interact with digoxin, warfarin and the low-dose contraceptive pill; however, adverse pharmacodynamic interactions with carbamazepine and topiramate have been demonstrated. Overall. Conclusion: Pharmacokinetic characteristics of levetiracetam are highly favourable and make its clinical use simple and straightforward. |

LEVETIRACETAM & WEIGHT GAIN

| Authors: | Patsalos PN. - Pharmacology and Therapeutics Unit, Department of Clinical and Experimental Epilepsy, Institute of Neurology/The National Hospital for Neurology and Neurosurgery, London, UK. P.Patsalos@ion.ucl.ac.uk |
| Summary: | Since 1989, eight new antiepileptic drugs (AEDs) have been licensed for clinical use. Levetiracetam is the latest to be licensed and is used as adjunctive therapy for the treatment of adult patients with partial seizures. AEDs. Pharmacokinetic studies of levetiracetam have been conducted in healthy volunteers, in adults, children and elderly patients with epilepsy, and in patients with renal and hepatic impairment. After oral ingestion, levetiracetam is rapidly absorbed, with peak concentration occurring after 1.3 hours, and its bioavailability is >95%. Co-ingestion of food slows the rate but not the extent of absorption. Levetiracetam is not bound to plasma proteins and has a volume of distribution of 0.5-0.7 L/kg. Plasma concentrations increase in proportion to dose over the clinically relevant dose range (500-5000 mg) and there is no evidence of accumulation during multiple administration. Steady-state blood concentrations are achieved within 24-48 hours. The elimination half-life in adult volunteers, adults with epilepsy, children with epilepsy and elderly volunteers is 6-8, 6-8, 5-7 and 10-11 hours, respectively. Approximately 34% of a levetiracetam dose is metabolised and 66% is excreted in urine unmetabolised; however, the metabolism is not hepatic but occurs primarily in blood by hydrolysis. Autoinduction is not a feature. As clearance is renal in nature it is directly dependent on creatinine clearance. Consequently, dosage adjustments are necessary for patients with moderate to severe renal impairment. To date, no clinically relevant pharmacokinetic interactions between AEDs and levetiracetam have been identified. Similarly, levetiracetam does not interact with digoxin, warfarin and the low-dose contraceptive pill; however, adverse pharmacodynamic interactions with carbamazepine and topiramate have been demonstrated. Overall. Conclusion: Pharmacokinetic characteristics of levetiracetam are highly favourable and make its clinical use simple and straightforward. |

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randomized, controlled clinical trials.
Authors: Gidal BE, Sheth RD, Magnus L, Herbeuval AF. - Department of Neurology, School of Pharmacy, University of Wisconsin, 777 Highland Ave., Madison, WI 53705, USA. beqidal@pharmacy.wisc.edu
Summary: Increases in body weight gain are important, and clinically significant adverse effects of several antiepileptic drugs (AED) including valproate and gabapentin. Weight gain may contribute to medication non-compliance, discontinuation, and importantly, may have secondary medical implications as well. Levetiracetam (LEV) is indicated for adjunctive treatment of partial seizures. The objective of the present evaluation was to examine the effects of LEV treatment on body weight in adult patients. METHODS: We analyzed data derived from four prospective, placebo-controlled randomized, clinical trials conducted in both in the US and Europe. Patients included in the present analysis were both men and women, greater than 16 years old, and who had LEV exposure for at least 1 month. Body weight was measured at baseline and at the final LEV study visit. Data are analyzed for all patients, by gender, body mass index (BMI), duration of LEV exposure and by concomitant AED treatment. Wilcoxon Signed Rank, or Rank Sum test used where appropriate, with significance assigned at P<0.05. Data are presented as mean values+1 S.D. RESULTS: Nine-hundred and seventy patients (age=37.5 years, 54% men/46% women) were evaluated. There were no significant differences in baseline demographics between LEV (n=631) or placebo (n=339) treated patient groups. Mean LEV dose and duration of treatment were 2053 mg/day (maximum dose of 4000 mg/day) and 125 days (maximum=181 days), respectively. Concomitant AED therapy included CBZ, PHT, VPA, PB, GBP, LTG, and VGB. For LEV-treated patients, no significant changes in body weight were noted. Mean body weight at baseline versus final study visit for LEV was 74.3+/-16.6 kg and 74.3+/-16.6 kg, respectively. For placebo-treated patients, baseline versus end of treatment weight was 72.4+/-15.4 kg and 72.7+/-15.9 kg, respectively, representing a slight, yet clinically trivial increase. Clinically significant weight change as defined as >7% change from baseline weight, occurred in 9% of LEV-treated patients (4.5% had increase in weight/4.5% decrease) versus 9.4% (5.9% had increase/3.5% decrease) in placebo-treated patients. Weight changes were not significantly different between groups. Neither baseline BMI, gender, or background AEDs, appeared to predispose to significant weight change for LEV-treated patients. Conclusion: We conclude that treatment with LEV at clinically relevant dosages is not associated with significant weight change. LEV would, therefore, appear to be a weight neutral AED.

levetiracetam & elderly patients
Tolerability of levetiracetam in elderly patients with CNS disorders.
Authors: Cramer JA, Leppik IE, Rue KD, Edrich P, Kramer G. - Department of Psychiatry, Yale University School of Medicine, 950 Campbell Avenue (G7E, Room 7-127), West Haven, CT 06516-2770, USA. Joyce.Cramer@Yale.Edu
Summary: The purpose of this analysis was to compare treatment-emergent adverse events (TEAE) related to use of levetiracetam (LEV) reported by young and elderly patients with anxiety and cognitive disorders, and young epilepsy patients. The LEV database includes reports of TEAE from trials of patients with diagnoses of a cognitive disorder (N=719), an anxiety disorder (N=1510), or localization-related epilepsy (N=1023) who participated in clinical trials lasting up to 16 weeks. Patients were grouped as young (<65 years) or elderly (65 years or = 65 years). The most common TEAE occurring most frequently in the LEV-treated groups were abdominal pain, asthenia, headache, anorexia, weight loss, dizziness, insomnia, somnolence, and tremor. The only significant differences in TEAE were seen between young and elderly groups with anxiety disorders (>3% higher for LEV than for placebo-treated patients) in headache (5.2% elderly, -0.9% young, P=0.041), and tremor (5.2 and -0.5%, respectively, P=0.022) and between young anxiety patients and young epilepsy patients for somnolence (-0.7 and 5.4%, respectively, P=0.036). For the other TEAEs there was no evidence for consistent differences between young and elderly patients and between patients with different CNS disorders. Conclusion: Overall, LEV was well tolerated by all patient groups. The favorable adverse event profile suggests that LEV might be suitable for use by elderly patients.

Levetiracetam, Tolerability & Efficacy
Safety profile of levetiracetam.
Authors: Arroyo S, Crawford P. - Medical College of Wisconsin, Milwaukee, Wisconsin 53226, United States. sarroyo@mcm.edu
Source: Epileptic Disord. 2003 May;5 Suppl 1:S57-63. Related Articles, Links
Summary: A good balance between safety and tolerability is necessary for an antiepileptic drug (AED) to be successful in the management of patients with epilepsy. Levetiracetam is one of the new generation of AEDs licensed as an add-on therapy for the treatment of patients with partial-onset seizures. Levetiracetam's mechanisms of action are not fully understood. Controlled clinical trials, open-label studies, and postmarketing surveillance indicate that levetiracetam has a favorable safety profile characterized by little effect on vital signs or clinical laboratory values, reported adverse events that are mild to moderate, and no known drug-drug interactions. The tolerability of levetiracetam may extend to both pediatric and elderly patients based on analyses of small numbers of patients. Tolerability is maintained over the long term. Levetiracetam does not appear to have a different safety profile in learning-disabled patients. Conclusion: Levetiracetam appears to have a good balance between tolerability and efficacy in the treatment of a wide variety of patients with partial epilepsy.

Levetiracetam & Pharmacokinetic
The ideal pharmacokinetic properties of an antiepileptic drug: how close does levetiracetam come?
Authors: Perucca E, Johannessen SI. - Clinical Pharmacology Unit, University of Pavia, Pavia, Italy. perucca@unipv.it
Summary: The pharmacokinetic properties of a drug are the primary deter-minant of the extent and duration of drug action, and influence susceptibility to clinically important drug interactions. Most of the older-generation antiepileptic drugs...
(AEDs) are far from ideal in terms of pharmacokinetics and interaction potential. For example, phenytoin, carbamazepine, and valproic acid exhibit non-linear kinetics; carbamazepine and valproic acid have relatively short half-lives; and most of these drugs cause either enzyme induction (phenytoin, phenobarbital, primidone, carbamazepine) or enzyme inhibition (valproic acid). Compared with older agents, certain new-generation AEDs offer a num-ber of pharmacokinetic advantages, particularly in terms of reduced inter-patient variability in drug clearance and a lower interaction potential. One of the most recently developed of these drugs, levetiracetam, comes especially close to fulfilling the desirable pharmacokinetic characteristics for an AED: (1) it has a high oral bioavailability, which is unaffected by food; (2) it is not significantly bound to plasma proteins; (3) it is eliminated partly in unchanged form by the kidneys and partly by hydrolysis to an inactive metabolite, without involvement of oxidative and conjugative enzymes; (4) it has linear kinetics; and (5) it is not vulnerable to important drug interactions, nor does it cause clinically significant alterations in the kinetics of concomitantly administered drugs. Although its half-life is relatively short (6 to 8 hours), its duration of action is longer than anticipated from its pharmacokinetics in plasma, and a twice-daily dosing regimen is adequate to produce the desired response.

**Levetiracetam & PAE**

- **Psychiatric adverse events during levetiracetam therapy.**
  
  **Authors:** Mula M, Trimble MR, Yuen A, Liu RS, Sander JW. - Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, UK.
  
  **Source:** Neurology. 2003 Sep 9;61(5):704-6. Related Articles, Links
  
  **Summary:** The prevalence and psychopathologic features of psychiatric adverse events (PAE) in 517 patients taking levetiracetam (LEV) were investigated. Fifty-three (10.1%) patients developed PAE. A significant association was found with previous psychiatric history, history of febrile convulsions, and history of status epilepticus, whereas lamotrigine co-therapy had a protective effect. Conclusion: PAE were not related to the titration schedule of LEV, and certain patients seem to be biologically more vulnerable.

**Levetiracetam & Acute Mania**

- **Levetiracetam in the treatment of acute mania: An open add-on study with an on-off-on design.**
  
  **Authors:** Grunze H, Langosch J, Born C, Schaub G, Walden J. - Department of Psychiatry at the University of Munich, Germany. grunze@psy.med.uni-muenchen.de
  
  **Source:** J Clin Psychiatry. 2003 Jul;64(7):781-4. Related Articles, Links
  
  **Summary:** BACKGROUND: Levetiracetam is a novel antiepileptic drug with a broad spectrum of efficacy in epilepsy. We have tested the antimanic properties of the drug as an add-on to haloperidol in an open trial. METHOD: After giving informed written consent, 10 bipolar I acute mania (DSM-IV) inpatients were investigated in an on-off-on study design. All patients were treated with 5 to 10 mg/day of haloperidol, depending on tolerability, throughout the investigation. Levetiracetam (up to 4000 mg/day) was added until day 14, then discontinued and reintroduced at day 21. The psychopathologic changes were assessed with the Young Mania Rating Scale (YMRS). RESULTS: After a mean decrease of the YMRS scores from 29.6 to 17.2 during the first "on" phase, manic symptoms worsened during the "off" period (YMRS score 20.9) and ameliorated again during the second "on" phase, with a decrease of the mean YMRS score to 14.7 at the end of the study. The mean dose of levetiracetam was 3125 mg/day. At day 14, only 2 (20%) of 10 patients were responders (defined as a decrease in YMRS scores of 50%) compared with 7 (70%) of 10 responders at the end of the study at day 28. Conclusion: The results from this open on-off-on add-on study suggest that levetiracetam exhibited additional antimanic effects. Controlled studies are clearly required.

**Levetiracetam & N-Type Calcium Channels**

- **Epilepsia: Selective Blockade of N-Type Calcium Channels by Levetiracetam**
  
  **Authors:** E. A. Lukyanetz, V. M. Shkryl, and P. G. Kostyuk
  
  **Source:** Volume 43 Issue 1 Page 9 - January 2002
  
  **Doi:**10.1046/j.1528-1157.2002.24501.x
  
  **Summary:** We investigated the effect of the new antiepileptic drug (AED) levetiracetam (LEV) on different types of high-voltageactivated (HVA) Ca2+ channels in freshly isolated CA1 hippocampal neurons of rats. Methods: Patch-clamp recordings of HVA Ca2+ channel activity were obtained from isolated hippocampal CA1 neurons. LEV was applied by gravity flow from a pipette placed near the cell, and solution changes were made by electromicrovalves. Ca2+ channel blockers were used for separation of the channel subtypes. Results: The currents were measured in controls and after application of 1200 M LEV. LEV irreversibly inhibited the HVA calcium current by 18% on the average. With a prepulse stimulation protocol, which can eliminate direct inhibition of Ca2+ channels by G proteins, we found that G proteins were not involved in the pathways underlying the LEV inhibitory effect. This suggested that the inhibitory effect arises from a direct action of LEV on the channel molecule. The blocking mechanism of LEV was not related to changes in steady-state activation or inactivation of Ca2+ channels. LEV also did not influence the rundown of the HVA Ca2+ current during experimental protocols lasting 10 min. Finally, LEV at the highest concentration used (200 M) did not influence the activity of L-type or Q-type Ca2+ channels in CA1 neurons, while selectively influencing the activity of N-type calcium channels. The maximal effect on these channels separated from other channel types was 37%. Conclusion: Our results provide evidence that LEV selectively inhibits N-type Ca2+ channels of CA1 pyramidal hippocampal neurons. These data suggest the existence of a subtype of N-type channels sensitive to LEV, which might be involved in the molecular basis of its antiepileptic action.

**Levetiracetam & Pharmacokinetics**

- **Epilepsia: Pharmacokinetics of Levetiracetam**
  
  **Authors:** Rodney A. Radtke
  
  **Source:** Volume 42 Issue s4 Page 24 - August 2001
doi:10.1046/j.1528-1157.2001.0420s4024.x
  
  **Summary:** Major considerations in the acceptance and impact of new antiepileptic drugs include their pharmacokinetics and their potential for interaction with other drugs. The
pharmacokinetics of levetiracetam, a newly approved add-on antiepileptic agent for partial-onset seizures in adults, has been evaluated in 27 phase I and II studies. Conclusion: Consistent findings in these studies include rapid and complete oral absorption, linear dose kinetics, a minimal degree of protein binding, and predominantly renal excretion. Because of the lack of hepatic metabolism and low protein binding, the risk of interaction with other drugs is considered low.

**SSRIs & Breastfeeding**

- **Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes.**

  **Authors:** Berle JO, Steen VM, Aarno TO, Breilid H, Zahlken K, Spigset O. - Centre for Child and Adolescent Mental Health, University of Bergen, Bergen, Norway. jean.berle@psyk.uib.no

  **Source:** J Clin Psychiatry. 2004 Sep;65(9):1228-34. Related Articles, Links

  **Summary:** BACKGROUND: The aims of the study were to quantify the drug exposure in breastfed infants of antidepressant-treated mothers, to identify possible adverse events, and to correlate these variables to maternal and infant drug metabolism-relevant genotypes and milk triglyceride content. METHOD: The study included 25 lactating women treated with citalopram (N = 9), sertraline (N = 6), paroxetine (N = 6), fluoxetine (N = 1), or venlafaxine (N = 3) and their 26 breastfed infants. Drug concentrations in maternal and infant serum and milk were analyzed using liquid chromatography mass spectrometry methods; milk triglyceride levels were measured with a commercial kit. Cytochrome P450 (CYP) 2D6 and CYP2C19 activity was determined by polymerase chain reaction-based genotyping of the mothers and infants. An infant adverse event questionnaire was completed by the medication-treated mothers as well as by a control group of medication-free breastfeeding mothers of 68 infants. RESULTS: Sertraline and paroxetine were not detected in any of the drug-exposed infants. The infant serum level of citalopram was either undetectable (N = 4) or low (N = 6). All venlafaxine-exposed infants had measurable drug concentrations. We identified a paroxetine-treated mother and her infant who were both CYP2D6 poor metabolizers, as well as a citalopram-treated mother with CYP2C19 poor metabolizer status, but the serum drug levels of their infants were still either undetectable (paroxetine) or low (citalopram). There was no evidence of adverse events in the drug-exposed infants. Conclusion: Serum drug levels in breastfed infants of antidepressant-treated mothers were undetectable or low. This study adds further evidence to previously published data indicating that breastfeeding should not be generally discouraged in women using serotonin reuptake inhibitor anti-depressants.

**Anxiety & Antidepressants**

- **Antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes.**

  **Authors:** Berle JO, Steen VM, Aarno TO, Breilid H, Zahlken K, Spigset O. - Centre for Child and Adolescent Mental Health, University of Bergen, Bergen, Norway. jean.berle@psyk.uib.no

  **Source:** J Clin Psychiatry. 2004 Sep;65(9):1228-34. Related Articles, Links

  **Summary:** BACKGROUND: The aims of the study were to quantify the drug exposure in breastfed infants of antidepressant-treated mothers, to identify possible adverse events, and to correlate these variables to maternal and infant drug metabolism-relevant genotypes and milk triglyceride content. METHOD: The study included 25 lactating women treated with citalopram (N = 9), sertraline (N = 6), paroxetine (N = 6), fluoxetine (N = 1), or venlafaxine (N = 3) and their 26 breastfed infants. Drug concentrations in maternal and infant serum and milk were analyzed using liquid chromatography mass spectrometry methods; milk triglyceride levels were measured with a commercial kit. Cytochrome P450 (CYP) 2D6 and CYP2C19 activity was determined by polymerase chain reaction-based genotyping of the mothers and infants. An infant adverse event questionnaire was completed by the medication-treated mothers as well as by a control group of medication-free breastfeeding mothers of 68 infants. RESULTS: Sertraline and paroxetine were not detected in any of the drug-exposed infants. The infant serum level of citalopram was either undetectable (N = 4) or low (N = 6). All venlafaxine-exposed infants had measurable drug concentrations. We identified a paroxetine-treated mother and her infant who were both CYP2D6 poor metabolizers, as well as a citalopram-treated mother with CYP2C19 poor metabolizer status, but the serum drug levels of their infants were still either undetectable (paroxetine) or low (citalopram). There was no evidence of adverse events in the drug-exposed infants. Conclusion: Serum drug levels in breastfed infants of antidepressant-treated mothers were undetectable or low. This study adds further evidence to previously published data indicating that breastfeeding should not be generally discouraged in women using serotonin reuptake inhibitor anti-depressants.

**Diabetes & Antipsychotics**

- **Antipsychotic treatment and sexual functioning in first-time neuroleptic-treated schizophrenic patients.**

  **Authors:** Bitter I, Basson BR, Dossenbach MR. - Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary BÉ. Lilly Regional Operations, Vienna, Austria CÉ. Lilly GmbH, Vienna, Austria.


  **Summary:** The present study examined sexual functioning among first-time treated schizophrenia patients at the time that they initiated antipsychotic treatment, and again 3 and 6 months later. These first-time treated patients comprise a subgroup of 570 schizophrenia patients who were part of a cohort of 7655 patients enrolled in the Intercontinental Schizophrenia Treatment Study. The objective of this study was to assess the pharmacokinetics of the antipsychotic aripiprazole when coadministered with lithium or valproate. Two open-label, sequential treatment design studies were conducted in chronically institutionalized patients with schizophrenia or schizoaffective disorder requiring treatment with lithium (n = 12) or valproate (divalproex sodium) (n = 10). Patients received aripiprazole 30 mg/day on days 1 to 14 and aripiprazole with concomitant therapy on days 15 to 36. Lithium was titrated from 900 mg until serum concentrations reached 1.0 to 1.4 mEq/L for at least 5 days. Valproate was titrated to 50 to 125 mg/L. Coadministration with lithium increased mean C(max) and AUC values of aripiprazole by about 19% and 15%, respectively, whereas the apparent oral clearance decreased by 15%. There was no effect on the steady-state pharmacokinetics of the active metabolite of aripiprazole. Coadministration with valproate decreased the AUC and C(max) of aripiprazole by 24% and 26%, respectively, with minimal effects on the active metabolite. Conclusion: Therapeutic doses of lithium and valproax had no clinically significant effects on the pharmacokinetics of aripiprazole in patients with schizophrenia or schizoaffective disorder.
Outpatient-Health Outcomes observational study (IC-SOHO). As part of a clinical assessment conducted at entry to the study, and after 3 and 6 months of antipsychotic medication, patients were asked to rate their sexual functioning, and the investigator was asked to rate the extent to which the patient had neuroleptic-related loss of libido and sexual dysfunction. After being treated, patients treated with olanzapine showed the lowest prevalence of neuroleptic-induced sexual difficulties. At 3 months, there were significant differences between the treatment groups on neuroleptic-related loss of libido, neuroleptic-related sexual dysfunction and change in patient-rated sexual dysfunction. At 6 months, the difference between the groups on neuroleptic-related loss of libido was statistically significant. There were no significant differences between males and females. Many recent onset patients appear to suffer from problems of sexual functioning. Conclusion: Olanzapine may offer an advantage in this area.

SSRIs & Sensory Disturbances

- **Serotonin reuptake inhibitor induced sensory disturbances.**
  
  **Authors:** Praharaj SK. - Department of Psychiatry, Dr Ram Manohar Lohia Hospital, New Delhi, India.
  
  **Source:** Br J Clin Pharmacol. 2004 Dec;58(6):673-4. Related Articles, Links
  
  **Summary:** Serotonin reuptake inhibitor induced sensory disturbances are reported rarely in the literature. This case report describes numbness and dysmorphic symptoms in the upper facial area associated with fluoxetine. There is no previous report of such an adverse reaction with any serotonin reuptake inhibitor in the literature and this report is intended to draw attention towards these unusual adverse effects.

- **Appical neuroleptic & Analgesia**
  
  **Do the second-generation atypical neuroleptics have analgesic properties? A structured evidence-based review.**
  
  **Authors:** Fishbain DA, Cutler RB, Lewis J, Cole B, Rosomoff RS, Rosomoff HL. - Department of Psychiatry, University of Miami School of Medicine, Miami, Florida.
  
  **Source:** Pain Med. 2004 Dec;5(4):359-65. Related Articles, Links
  
  **Summary:** ABSTRACT Study Design. This is a structured, evidence-based review of all available studies on the potential effectiveness of the atypical neuroleptics for the treatment of pain (analgesia). Objectives. To determine what evidence, if any, exists for, or against, the effectiveness of the atypical neuroleptics for analgesia. Summary of Background Data. There has been significant controversy over whether the conventional neuroleptics (non-atypicals) have analgesic properties. A recent review (Patt et al. 1994) did conclude that the evidence for effectiveness was sparse, except for methotrexaprazine. However, that review did not include a new class of neuroleptics: the atypicals such as olanzapine, risperidone, quetiapine, etc. Methods. A computer and manual search for studies relating to the atypicals and their analgesic effectiveness produced 10 studies/reports. These were reviewed in detail, and information relating to the above problem was abstracted and placed into tabular form. Each report was also categorized by the type of study it represented according to the guidelines developed by the Agency for Health Care Policy and Research (AHCPR). The strength and consistency of the evidence represented by the 10 studies were then categorized according to the AHCPR guidelines. Conclusion: of this review were based on these results. Results of Data Synthesis. Of the 10 studies/reports, four were characterized by AHCPR guidelines as Type II (experimental), two were Type III (quasieperimental), two were Type IV (nonexperimental), and two were Type V (case reports). Of these studies/reports, 90% indicated that the atypicals did have an analgesic effect. The overall strength and consistency of this evidence using the AHCPR guidelines was, therefore, categorized as B (generally consistent from Type II, Type III, and Type IV studies). Conclusions. Based on the above results, it was concluded that the reviewed data were generally consistent, suggesting that some of the atypicals may have an analgesic effect. There were, however, few double-blind, placebo-controlled studies, and many of the reports/studies had less than 50 patients. As such, this question requires further research.

**Donepezil, Safety & Tolerability**

- **The safety and tolerability of donepezil in patients with Alzheimer's disease.**
  
  **Authors:** Jackson S, Ham RJ, Wilkinson D. - Department of Health Care of the Elderly, Guy's, King's and St Thomas' School of Medicine, Kings College London, London, UK.
  
  
  **Summary:** Cholinesterase (ChE) inhibitors, which prevent the hydrolysis of acetylcholine, have been approved for the symptomatic treatment of Alzheimer's disease (AD) for over a decade. However, the first ChE inhibitors were associated with a high incidence of side-effects and general tolerability concerns, including hepatotoxicity. Side-effects associated with increased cholinergic activity, particularly in the gastrointestinal (GI) system, can prevent patients from achieving effective doses of drug. In addition, the advanced age and frail nature of patients with AD mean that poor tolerability is a serious concern. The potential for drug-drug interactions is also an important consideration, due to the high prevalence of comorbid disease in these patients. Data both from clinical trials and studies in routine clinical practice have shown that donepezil is associated with a low incidence of GI adverse events (AEs) that is comparable with placebo. Donepezil is a potent, selective inhibitor of acetylcholinesterase, and selective inhibition of central as opposed to peripheral ChEs might be expected to reduce the incidence of AEs, thus this may explain the lower incidence of cholinergic AEs observed following treatment with donepezil, compared with nonselective ChE inhibitors. There are no differences in cardiovascular AEs, including bradycardia, between placebo and donepezil groups in the clinical trials published to date, even in a very sick vascular dementia population with high rates of comorbidity and concomitant medication use. Data from single- and multiple-dose studies of donepezil in patients with hepatic impairment and with moderately to severely impaired renal function indicate that donepezil is safe and well tolerated in these groups. Furthermore, both in vitro and clinical studies have shown that donepezil is not associated with drug-drug interactions. The incidence of weight loss is very similar between donepezil- and placebo-treated patients. Although insomnia and other sleep disorders have been reported following administration of...
donepezil, lengthening the time period before increasing the dose of donepezil from 5 to 10 mg day(-1) or switching to morning dosing can reduce these events to the levels of placebo-treated patients. Over 770 million days of patient use and an extensive publication database demonstrate that donepezil has a good tolerability and safety profile.

**Injectable Risperidone & Long-acting**

* Long-acting injectable risperidone.

**Authors:** Ehret MJ, Fuller MA. - Cleveland Department of Veterans Affairs Medical Center, 10000 Brecksville Rd., Brecksville, OH 44141-3204, USA.


**Summary:** Objective: To review the pharmacology, pharmacokinetics, clinical efficacy, and safety profile of long-acting (LA) risperidone for the treatment of schizophrenia. Data Sources: Information was selected from PubMed (1965-July 2004). Applicable scientific posters were also used. Study Selection And Data Extraction: All published information on risperidone LA was considered. Material providing a comprehensive description was considered. Data Synthesis: Risperidone LA is the first long-acting, injectable atypical antipsychotic. It is dosed at 25-50 mg every 2 weeks. Adverse effects are similar to those seen with oral risperidone. A short-term study showed that risperidone LA is better than placebo in reducing the signs and symptoms of schizophrenia, and a long-term trial showed that stable schizophrenic patients can be switched from either oral or other injectable antipsychotic medications to risperidone. Conclusion: Risperidone LA is efficacious and safe in the treatment of schizophrenia.

**New SNRI & Duloxetine**


**Authors:** Rabasseda X. - Medical Information Department, Prous Science, Barcelona, Spain. xrabasseda@prous.com

**Source:** Drugs Today (Barc). 2004 Sep;40(9):773-90. Related Articles, Links

**Summary:** Double-blind, placebo-controlled clinical trials have evaluated and demonstrated the efficacy of duloxetine as an antidepressant in patients with major depressive disorders. The drug has been noted to be well tolerated and effective in the control of depressive symptoms. In addition, duloxetine has been shown to be better than placebo and as effective as paroxetine as an antidepressant and also better than placebo for reducing pain in both experimental models and patients. Conclusion: Duloxetine is a safe and well-tolerated new treatment option for depression including anxiety and painful physical symptoms. Furthermore, duloxetine has proven robust efficacy in stress urinary incontinence.

**Epilepsy & Antiepileptics**

* Efficacy and tolerability of the new antiepileptic drugs: comparison.

**Authors:** Beghi E. - Epilepsy Center, University of Milano-Bicocca, Ospedale San Gerardo, Monza, Italy. beghi@marionegri.it

**Source:** Lancet Neurol. 2004 Oct;3(10):618-21. Related Articles, Links

**Summary:** BACKGROUND: Until the early 1990s six major compounds (carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid) were available for the treatment of epilepsy. However, these drugs have pharmacokinetic limitations, teratogenic potential, and a negative effect on cognitive functions that impairs the quality of patients’ lives and limits the use of these drugs in some patients. In addition, 20-30% of patients are refractory to these drugs. RECENT DEVELOPMENTS: The development of ten new antiepileptic drugs (vigabatrin, felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, and pregabalin) has expanded treatment options. The newer drugs may be better tolerated, have fewer drug interactions, and seem to affect cognitive functions to a lesser extent than old drugs. Guidelines on the use of new antiepileptic drugs have been developed in the USA and in the UK. Both guidelines offer a clear picture of the efficacy, safety, and tolerability of the new antiepileptic drugs and agree on their use as add-on treatment in patients who do not respond to conventional drugs. The guidelines differ in the type and strength of recommendations. Whereas the US guidelines recommend treatment in newly diagnosed epilepsy with a standard drug or a new drug depending on the individual patient’s characteristics, the UK guidelines recommend that a new antiepileptic drug should be considered only if there is no benefit from an old antiepileptic drug, an old drug is contraindicated, there is a previous negative experience with the same drug, or the patient is a woman of childbearing potential. WHERE NEXT: The limited amount of information on the new antiepileptic drugs may explain the discrepancies among the two guidelines and between these and other recommendations. Comparative, pragmatic, long-term and open trials should be done to show long-term efficacy and comparative features of the new antiepileptic drugs, and to better assess the effect on quality-of-life, cost-effectiveness, tolerability, and teratogenic potential. In addition, the conflicts should be resolved between the needs of the regulatory bodies and those of the treating physicians. Finally, there is a need for trial designs to be standardised.

**Levetiracetam & Epilepsy**

* Levetiracetam: treatment in epilepsy.

**Authors:** Ben-Menachem E. - University of Gotебorg, Sahlgren Hospital, Goteborg, Sweden. ebm@neuro.gu.se

**Source:** Expert Opin Pharmacother. 2003 Nov;4(11):2079-88. Related Articles, Links

**Summary:** A large number of new antiepileptic drugs (AEDs) have become available over the last 10 years. Results from placebo-controlled clinical trials and community-based practice have demonstrated that levetiracetam has a broad spectrum of activity in suppressing seizures as add-on treatment and monotherapy and that it is safe and well-tolerated. Levetiracetam also has a favourable pharmacokinetic profile characterised by rapid and nearly complete absorption, very low potential for drug interactions and a prolonged
pharmacodynamic effect that permits twice-daily dosing. **Conclusion**: Although, the mechanism of action of levetiracetam is not completely understood, preclinical studies suggest that it may have antiepileptogenic and neuroprotective effects, with the potential to slow or arrest disease progression.

### Levetiracetam & Optimal Choice

**Role of levetiracetam in the treatment of epilepsy.**

**Authors**: Brodie MJ, French JA. - Epilepsy Unit, Division of Cardiovascular and Medical Sciences, Western Infirmary, Glasgow, Scotland, United Kingdom.

**Source**: Epileptic Disord. 2003 May;5 Suppl 1:S65-72. Related Articles, Links

**Summary**: Physicians treating patients with epilepsy have a host of therapeutically options. Drug choice is dictated first by the seizure(s) and/or epilepsy syndrome. Age is also a factor. Special considerations apply to women, particularly during their childbearing years, and to patients who are learning-disabled. Drug selection is further influenced by such characteristics as spectrum of activity, rapid response, low potential for drug-drug interactions, and ease of use. In addition to clinical trial data, postmarketing assessments of the new antiepileptic drugs provide useful clinical information on efficacy and safety. **Conclusion**: Levetiracetam has specific characteristics that make it an optimal choice for many patient populations.

### Levetiracetam, Monotherapy & Refractory partial seizures

**Preliminary efficacy of levetiracetam in monotherapy.**

**Authors**: Ben-Menachem E. - University of Goteborg, Sahlgren Hospital, Goteborg, Sweden, ehm@neuro.gu.se

**Source**: Epileptic Disord. 2003 May;5 Suppl 1:S51-5. Related Articles, Links

**Summary**: The standard of care for prescribing antiepileptic drugs (AEDs) has come to favor the use of monotherapy when possible; i.e., when comappable efficacy can be achieved with fewer risks of adverse events and drug interactions. Most patients with epilepsy are started on one of the classic AEDs and, if it proves ineffective, another drug is tried, usually as monotherapy. While most of the newer AEDs that have come into clinical use in recent years are initially used as add-on therapy, their success at improving seizure control in combination treatments has led to their cautious use as monotherapy even before they have been approved for this indication. As a first study to determine the potential efficacy of levetiracetam in monotherapy, a withdrawal trial model was used. Patients who achieved adequate seizure control with levetiracetam as add-on therapy in a double-blind, placebo-controlled study entered a monotherapy phase of the trial in which the baseline AED was gradually withdrawn. Also, long-term data of 505 patients who received levetiracetam for refractory partial seizures were reviewed and found to include 49 patients still treated with levetiracetam monotherapy at the end of the study for a duration between 3 months and 5.5 years. **Conclusion**: Data from patients in the two trials lend supportive evidence that levetiracetam monotherapy is safe and effective for partial seizures.

### Levetiracetam & Long-term Experience

**Long-term experience with levetiracetam.**

**Authors**: Abou-Khalil B, Lazenby B. - Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee 37232-3375, United States.

**Source**: Epileptic Disord. 2003 May;5 Suppl 1:S33-7. Related Articles, Links

**Summary**: Although short-term clinical trials provide important data regarding efficacy and tolerability, long-term studies are needed to address important aspects of clinical practice, such as long-term efficacy and safety. Long-term studies and postmarketing data show that the efficacy of levetiracetam is sustained over the long term and that this antiepileptic drug continues to be well tolerated, with low withdrawal rates and high retention rates. Patients continue to achieve significant reductions in seizure frequency and may achieve seizure freedom. **Conclusion**: Levetiracetam may allow patients to decrease the number of concomitant antiepileptic medications or withdraw to monotherapy. Add-on therapy with levetiracetam should be considered when additional control of seizures is needed.

### New AEDs

**New antiepileptic drug therapies.**

**Authors**: Bergin AM, Connolly M. - Division of Epilepsy and Clinical Neurophysiology, Children's Hospital, 300 Longwood Avenue, HU2, Boston, MA 02115, USA.


**Summary**: The introduction of these new antiepileptic drugs, from felbamate to levetiracetam, raised hope of control of epilepsy with fewer adverse effects and improved quality of life. Unfortunately, many patients continue to experience refractory epilepsy despite the use of these new agents, and dose-related adverse effects and idiosyncratic reactions continue to be problematic. A recent report describes six new compounds in preclinical development, and five in clinical trials [131]. As the number of available, effective, but imperfect antiepileptic drugs increases, many challenges remain. These include: choosing the drug appropriate for the epileptic syndrome, assessing accurately the range of a drug's adverse effects in an individual patient, and considering carefully the drug's interactions in combination drug therapy. In considering drug combinations, differing mechanisms of drug action and favorable pharmacodynamic interactions (an area requiring additional studies) are of importance. **Conclusion**: Clinicians caring for children who have epilepsy anticipate further advances in the pharmacogenetics and molecular pathophysiology of epilepsy, leading to individually tailored, effective, and safe therapy.

### Anxiety: PTSD, OCD, SP & GAD

**An open-label study of levetiracetam for the treatment of social anxiety disorder.**

**Authors**: Simon NM, Worthington JJ, Doyle AC, Hoge EA,
Kinrys G, Fischmann D, Link N, Pollack MH. - Center for Anxiety and Traumatic Stress Related Disorders, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA.  
Source: J Clin Psychiatry. 2004 Sep;65(9):1219-22. Related Articles, Links  
Summary: OBJECTIVE: Social anxiety disorder is a disabling condition characterized by excessive fear and avoidance of social and performance situations. While a variety of effective pharmacotherapies exists, many patients do not fully respond to or tolerate available agents. Preclinical and early clinical experience with levetiracetam, a novel anticonvulsant agent, suggests that levetiracetam has anxiolytic properties and a favorable adverse event profile. Levetiracetam thus warrants systematic evaluation as a treatment option for anxiety disorders. METHOD: Twenty adult outpatients who were recruited through advertisement and clinical referral and who met DSM-IV criteria for social anxiety disorder, generalized type, participated in this 8-week open-label, flexible-dose study from November 2002 to December 2003. Participants were required to have scores of >/= 50 on the Liebowitz Social Anxiety Scale (LSAS) and >/= 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S) at baseline. The presence of comorbid depression and anxiety disorders were permitted as long as social anxiety disorder was the primary disorder. Levetiracetam was initiated at 250 mg/day for the first week and flexibly titrated up to a maximum of 3000 mg/day (1500 mg b.i.d.). The primary outcome measure was change in the LSAS score at endpoint. RESULTS: There was a clinically significant 20.5-point decrease in LSAS scores in the intent-to-treat, last-observation-carried-forward analysis (t = 3.1; p < .01, N = 20). There were also significant reductions in CGI-S (p < .01) and Hamilton Rating Scale for Anxiety (p < .02) scores. Conclusion: This pilot study supports the safety and potential efficacy of a novel agent, levetiracetam, for the treatment of social anxiety disorder. Larger controlled trials are warranted to confirm these results.

Resistant OCD & Strategies for Treatment  
- Pharmacological augmentation strategies for treatment-resistant obsessive-compulsive disorder.

Authors: Walsh KH, McDougle CJ. - Department of Psychiatry, Indiana University School of Medicine, Riley Hospital for Children, Room 4300, 702 Barnhill Drive, Indianapolis, IN 46202, USA. kewalsh@iupui.edu  
Summary: First-line treatment for obsessive-compulsive disorder (OCD) has been well-established for over a decade although newer medications, such as citalopram and venlafaxine, have emerged to take a place among the older, more established serotonin re-uptake inhibitors (SRIs). Unfortunately, as many as 50% of all patients with OCD will have symptoms refractory to a single medication treatment trial, and a smaller percentage will remain refractory after two or more trials. The optimal dosage and duration for first-line trials have been established. Many strategies exist for patients who do not respond to first- or second-line medication trials, including behavioural therapy, switching to newer SRIs, and augmentation with additional medications. Conclusion: This review will focus on medication strategies for augmenting SRI treatment response in OCD treatment, including neuroleptic and serotonergic agents. Future investigations should include more controlled studies and investigate medications that are less likely to trigger extrapyramidal symptoms, diabetes mellitus and weight gain.

Hypermobility & Anxiety  
- Is joint hypermobility related to anxiety in a nonclinical population also?

Authors: Bulbena A, Agullo A, Pailhez G, Martin-Santos R, Porta M, Guitart J, Gago J. - Department of Psychiatry, Hospital del Mar, Barcelona, Spain. abulbena@acmcb.es  
Source: Psychosomatics. 2004 Sep-Oct;45(5):432-7  
Summary: This study examines the association between joint hypermobility syndrome and anxiety in a nonclinical sample. Subjects (N = 526) receiving a medical check-up were assessed with the Hospital del Mar hypermobility criteria and the State-Trait Anxiety Inventory. Scores for trait anxiety, and to a lesser extent state anxiety, were significantly higher among subjects with joint hypermobility syndrome than among subjects without this syndrome (median trait anxiety scores for women: 17 versus 11; median scores for men: 13 versus 1). These findings indicate that the association of joint hypermobility syndrome and anxiety holds even for subjects with no psychiatric diagnosis. Therefore, it seems that this benign connective tissue disorder is a predisposing factor for trait anxiety. However, it is necessary to further explore and define the biological basis of this syndrome, as well as its associations and clinical expressions, which interact with great complexity.

PTSD, Depression & September 11  
- Posttraumatic stress disorder, depression, and perceived safety 13 months after September 11.

Authors: Greeger TA, Fullerton CS, Ursano RJ. - Uniformed Services University of the Health Sciences, Department of Psychiatry, B3068, 4301 Jones Bridge Road, Bethesda, Maryland 20814. thomas.grieger@na.amedd.army.mil  
Source: Psychol Serv. 2004 Sep;55(9):1061-3  
Summary: This study assessed relationships between exposure to the September 11, 2001, terrorist attack, current posttraumatic stress disorder (PTSD), current major depression, and current safety perceptions in a sample of 212 Pentagon staff members 13 months after the attack. Forty-eight respondents (23 percent) had possible PTSD; eight (4 percent) had probable major depression. Respondents who were directly exposed to the attack were more likely to have PTSD and major depression and were less likely to have a perception of safety at work and in usual activities and travel only. In contrast, respondents with PTSD reported a lower perception of safety at home, at work, and in usual activities and travel.

Hypochondriasis diagnosis  
- A new, empirically established hypochondriasis diagnosis.

Authors: Fink P, Ortbeln E, Toft T, Sparer KC, Frostholm L, Olesen F. - Research Unit for Functional Disorders, Aarhus University Hospital, DK-8000 Aarhus C, Denmark. flip@akh.aaa.dk  
Source: Am J Psychiatry. 2004 Sep;161(9):1680-91  
Summary: OBJECTIVE: The narrow ICD-10 and DSM-IV definition of hypochondriasis makes it rarely used yet does not prevent extensive diagnosis overlap. This study identified a
distinct hypochondriasis symptom cluster and defined diagnostic criteria. METHOD: Consecutive patients (N=1,785) consulting primary care physicians for new illness were screened for somatization, anxiety, depression, and alcohol abuse. A stratified subgroup of 701 patients were interviewed with the Schedules for Clinical Assessment in Neuropsychiatry and questions addressing common hypochondriasis symptoms. Symptom patterns were analyzed by latent class analysis. RESULTS: Patients fell into three classes based on six symptoms: preoccupation with the idea of harboring an illness or with bodily function, rumination about illness, suggestibility, unrealistic fear of infection, fascination with medical information, and fear of prescribed medication. All symptoms, particularly rumination, were frequent in one of the classes. Classification allowed definition of new diagnostic criteria for hypochondriasis and division of the cases into “mild” and “severe.” The weighted prevalence of severe cases was 9.5% versus 5.8% for DSM-IV hypochondriasis. Compared with DSM-IV hypochondriasis, this approach produced less overlap with other somatoform disorders, similar overlap with nonsomatoform psychiatric disorders, and similar assessments by primary care physicians. Severe cases of the new hypochondriasis lasted 2 or more years in 54.3% of the subjects and 1 month or less in 27.2%. Conclusions: These results suggest that rumination about illness plus at least one of five other symptoms form a distinct diagnostic entity performing better than the current DSM-IV hypochondriasis diagnosis. However, these criteria are preliminary, awaiting cross-validation in other subject groups.

Refractory OCD; PP & Quetiapine

Obessive-compulsive disorder in the postpartum: open-label trial of quetiapine augmentation.

Authors: Misi S, Milis L. - Department of Psychiatry, University of British Columbia, British Columbia, Canada. smisi@providencehealth.bc.ca


Summary: OBJECTIVE: Postpartum nonpsychotic conditions are routinely treated with antidepressant therapy. However, a subset of this population with comorbid obsessive-compulsive disorder (OCD) is treatment-resistant. Optimal response is obtained by augmentation therapy with novel antipsychotics. The objective of this open-label study was to evaluate clinical response to quetiapine augmentation of SSRIs or SNRIs in treatment-resistant OCD in the postpartum. METHODS: Twenty-two postpartum women diagnosed with OCD as per DSM-IV criteria, who did not respond to at least 6 weeks of SSRI or SNRI monotherapy, were offered a trial of quetiapine augmentation for 12 weeks. Response (defined as >50% reduction in scores) was assessed using the Yale Brown Obsessive-Compulsive Scale (YBOCS) and Clinical Global Impressions scale (CGI). RESULTS: Seventeen patients agreed to a trial of quetiapine augmentation. Three withdrew early due to side effects, and 14 completed the 12-week trial. Of these, 11 responded to treatment within 12 weeks, with a mean (SD) response time of 5.9 (2.6) weeks. The mean (SD) baseline YBOCS score of 24.7 (6.8) dropped to a mean of 10.3 (9.0), with a mean reduction of 59.6%. Mean CGI scores at outcome were 1.9 (1.2). The average dose of response was 112.5 mg (76.4 mg). Sedation was the most commonly reported side effect. Conclusion: Although limited by lack of controls, this is the first study in a postpartum population where the addition of quetiapine to antidepressant therapy has been shown to be effective for treatment-refractory OCD. Quetiapine deserves further controlled study in this context.

OCD & Venlafaxine

The Role of Venlafaxine in the Treatment of Obsessive-Compulsive Disorder (January).

Authors: Phelps NJ, Cates ME. - Western Missouri Mental Health Center, Kansas City, MO.


Summary: OBJECTIVE: To evaluate the published literature regarding the use of venlafaxine in the treatment of obsessive-compulsive disorder (OCD). DATA SOURCES: MEDLINE (1996-March 2004) and International Pharmaceutical Abstracts (1970-March 2004) were searched using the terms venlafaxine and obsessive-compulsive disorder. A bibliographic search was conducted as well. DATA SYNTHESIS: Successful treatment of OCD with venlafaxine has been reported in case reports, open trials, and blinded trials versus active comparators. The only placebo-controlled trial did not find statistically significant improvement with venlafaxine treatment; however, methodologic limitations may have influenced those results. Venlafaxine appears to be as efficacious as clomipramine, but is preferable to this agent in terms of safety and tolerability. Venlafaxine seems to be similar to paroxetine with respect to both therapeutic effects and adverse effects, but may be inferior to paroxetine when used for nonresponders to previous serotonin-reuptake inhibitor therapy. Conclusion: Although the relative scarcity of data precludes definitive conclusions, available evidence suggests that venlafaxine is effective and well tolerated in the treatment of OCD. Unfortunately, it has not shown any unique advantages relative to currently available medications.

Social Phobia & Neurobiology

[Neurobiology and Pharmacotherapy of Social Phobia.]

Article in French

Authors: Aouizerate B, Martin-Guehl C, Tignol J. - Service de Psychiatrie d'Adultes, (Professeur, Tignol) Universite Victor-Segalen Bordeaux 2, Ctr Hospitalier Charles-Perrens, Centre Carriere, 121, rue de la Bechade, 33076 Bordeaux


Summary: Social phobia (also known as social anxiety disorder) is still not clearly understood. It was not established as an authentic psychiatric entity until the diagnostic nomenclature of the American Psychiatric Association DSM III in 1980. In recent years, increasing attention among researchers has contributed to provide important information about the genetic, familial and temperamental bases of social phobia and its neurochemical, neuroendocrinological and neuroanatomical substrates, which remain to be further investigated. Up to date, there have been several findings about the possible influence of variables, including particularly genetic, socio-familial and early temperamental (eg behavioral inhibition) factors that represent risk for the later development of social phobia. Clinical neurobiological studies, based on the use of exogenous compounds such as lactate, CO2, caffeine, epinephrine,
flumazenil or cholecystokinin/pentagastrin to reproduce naturally occurring phobic anxiety, have shown that patients with social phobia appear to exhibit an intermediate sensitivity between patients with panic disorder and control subjects. No difference in the rate of panic attacks in response to lactate, low concentrations of CO2 (5%), epinephrine or flumazenil was observed between patients with social phobia and normal healthy subjects, both being less reactive compared to patients with panic disorder. However, patients with social phobia had similar anxiety reactions to high concentrations of CO2 (35%), caffeine or cholecystokinin/pentagastrin than those seen in patients with panic disorder, both being more intense than in controls. Several lines of evidence suggest specific neurotransmitter system alterations in social phobia, especially with regard to the serotoninergic, noradrenergic and dopaminergic systems. Although no abnormality in platelet serotonin transporter density has been found, patients with social phobia appear to show an enhanced sensitivity of both post-synaptic 5HT1A and 5HT2 serotonin receptor subtypes, as reflected by increased anxiety and hormonal responses to serotoninergic probes. Platelet 5HT2 receptor density has also been reported to be positively correlated to symptom severity in patients with social phobia. During anticipation of public speaking, heart rate was elevated in patients with social phobia compared to controls. Norepinephrine response to the orthostatic challenge test or to the Valsalva maneuver was also greater in patients with social phobia. While normal b-adrenergic receptor number was observed in lymphocytes, a blunted response of growth hormone to clonidine, an a2-adrenergic agonist, was reported. This suggests reduced post-synaptic a2-adrenergic receptor functioning related to norepinephrine overactivity in social phobia. Decreased cerebrospinal fluid levels of the dopamine metabolite homovanillic acid have also been observed. There are relatively few reports of involvement of the adrenal and thyroid functions in social phobia, and all that has been noted is that patients with social phobia show an exaggerated adrenocortical response to a psychological stressor. Recent advances in neuro-imaging have contributed to find low striatal dopamine D2 receptor binding or low dopamine transporter site density in patients with social phobia. They have also demonstrated the involvement of the corticlimbic pathways, including the prefrontal cortex, hippocampus and amygdala, which show an increased activity in different experimental conditions. These brain regions have extensively been reported to play an important role in the cognitive appraisal in determining the significance of environmental stimuli, in the emotional and mnemonic integration of information, and in the expression of contextual fear-conditioned behaviors, which might be disrupted in the light of the phenomenological aspects of social phobia. A substantial body of literature based on case reports, open and placebo-controlled trials, has now clearly examined the efficacy of major classes of psychotropic agents including monoamine oxidase inhibitors, b-blockers, selective serotonin reuptake inhibitors and benzodiazepines in social phobia. Until recently, irreversible non-selective monoamine oxidase inhibitors, of which phenelzine was the most extensively evaluated, were considered as the most efficacious treatment in reducing the symptomatology associated with social phobia in 50-70% of cases after 4 to 6 weeks. However, side effects and dietary restrictions limit their use. This led to the development of reversible inhibitors of monoamine oxidase A, for which careful dietary monitoring is not required. Moclobemide has been the most widely studied but produced unconvincingly therapeutic effects on social phobic symptoms. To date, selective serotonin reuptake inhibitors may be considered as a reasonable first-line pharmacotherapy for social phobia. There is growing evidence for the efficacy of the selective serotonin reuptake inhibitors fluvoxamine, fluoxetine, citalopram, paroxetine and sertraline. They have beneficial effects with response rates ranging from 50 to 80% in social phobia. It has been recommended that the treatment period should be extended at least 6 months beyond the early improvement achieved within the first 4 to 6 weeks. The overall advantages include tolerability with a low risk of adverse events. The benzodiazepines clonazepam and alprazolam have also been proposed for the treatment of social phobia. Symptomatic relief occurred in 40 to 80% of the cases with a relatively rapid onset of action within the first two weeks. Untoward effects, discontinuation-related withdrawal symptoms and abuse or dependence liability constitute major concerns about the use of benzodiazepines, so they should be reserved for cases unresponsive to the safer medications cited above, b-blockers such as atenolol and propranolol have commonly been employed in performance anxiety, decrea-sing autonomic symptoms (eg, tachycardia, sweating and dry mouth). However, they are not effective in the generalized form of social phobia. Other pharmacologic alternatives seem helpful for the management of social phobia, including venlafaxine, gabapentin, bupropion, nefazodone or augmentation with buspirone. Preliminary studies point to promising effects of these agents. Larger controlled clinical trials are now needed to confirm their potential role in the treatment of social phobia.

Addiction

Recreational gambling –

Health correlates of recreational gambling in older adults.

Authors: Desai RA, Maciejewski PK, Dausey DJ, Caldarone BJ, Potenza MN. - Northeast Program Evaluation Center/182, 950 Campbell Ave., West Haven, CT 06516.
desai@biomed.med.yale.edu

Source: Am J Psychiatry. 2004 Sep;161(9):1672-9

Summary: OBJECTIVE: Prior studies have found high rates of alcohol use and abuse/dependence, depression, bankruptcy, and incarceration associated with recreational gambling. Despite growing rates of recreational gambling in older adults, little is known regarding its health correlates in this age group. The objective of this study was to identify health and well-being correlates of past-year recreational gambling in adults age 65 years and older, compared to adults age 18-64 years. METHOD: The Gambling Impact and Behavior Study surveyed by telephone a nationally representative sample of 2,417 adults. Multivariate analyses were used to compare past-year recreational gamblers and nongamblers in the older and younger age groups on measures of alcohol use and abuse/dependence, substance abuse/dependence, depression, mental health treatment, subjective general health, incarceration, and bankruptcy. Additional analyses compared the gambling patterns in older and younger adult past-year recreational gamblers.

RESULTS: After the effects of sociodemographic factors were controlled, older adult past-year recreational gamblers were more likely to report past-year alcohol use and better health than were older nongamblers. Multivariate analyses investigating interactions of gambling and age found that higher rates of good to excellent subjective general health in recreational gamblers were mainly attributable.
to the older age group. Older adult gamblers were more likely than younger adult gamblers to begin gambling after age 18 years, to gamble more frequently, and to report a larger maximum win. Conclusions: Recreational gambling patterns of older adults differ from those of younger adults. In contrast to findings in younger adults, recreational gambling in older adults is not associated with negative measures of health and well-being.

Dexamphetamine & Cocaine Dependence

Outpatient Treatment of Cocaine Dependence With Dexamphetamine

Authors: Moselhy, Hamdy F MBCh, MSc, DCP, MRCPsych *; El-Sheikh, Hussein MBCh, MSc, MD +
Source: Addictive Disorders & Their Treatment. 3(3):133-137, September 2004
Summary: Objectives: This research assessed the effect of prescribed dexamphetamine on cocaine users in a community in 2001. Methods: Case notes of all patients seen and prescribed medication by the consultant psychiatrist in the service were received. A matched age and sex control group was compared with subject group. Results: The mean age for the subject group was 31 years. The approximate number of days of using cocaine was 4 days per week. The mean amount of use in typical day was 2 g. The mean results of treatment showed that the mean dose of dexamphetamine was 25 mg daily. The retention in treatment was 5.6 months. Conclusion: Dexamphetamine treatment of cocaine dependence could help in reducing the amount of use and help in retention of the patient in the treatment service.

Addiction

Changes in Methadone Concentration, Opioid Effects, and Opioid Withdrawal During Induction Onto Maintenance Treatment

Authors: Athanasos, Peter BSc (Hons); Morrish, Glynn BSc (Hons); Somogyi, Andrew A PhD; Bochner, Felix MD, FRACP; White, Jason M PhD
Source: Addictive Disorders & Their Treatment. 3(3):122-128, September 2004
Summary: Objective: Deaths of people on methadone maintenance due to respiratory depression most commonly occur during the first week of dosing. This paper describes the changes in opioid withdrawal, respiratory rate, and pupil diameter that occur during the first 8 days of methadone treatment. The changes in plasma concentration of the active enantiomer, R-methadone, are also described and related to the changes in opioid effects and withdrawal. Methods: Five heroin-dependent subjects were assessed each day over the first 8 days of methadone administration. Blood samples were collected and measures made of withdrawal severity, respiration, and pupil diameter prior to methadone dosing and 3 hours after; additional sampling and testing were carried out on days 1, 3, 5, and 8. Blood samples were analyzed to determine the plasma concentration of R-methadone. Results: Over the first 8 days plasma concentration of R-methadone increased, withdrawal severity decreased, and both pupil diameter and respiratory rate decreased. Each of the 3 measures of opioid effect/withdrawal was significantly correlated with plasma R-methadone concentration. Conclusion: Caution needs to be exercised during the first days of methadone dosing as some degree of respiratory depression is common in non-problematic patients. Observation of patients around time of peak methadone concentration would reduce risk.

Alcoholism & Serotonergic System

Role of the serotonergic system in the neurobiology of alcoholism: implications for treatment.

Authors: Daniel Connor BA, University of Virginia Health System, Charlottesville, Virginia, USA
Summary: Preclinical studies have contributed greatly to our understanding of the neurochemical pathways associated with the development and maintenance of alcohol-seeking behaviour. These studies have demonstrated the important role of serotonergic pathways, particularly as they relate to dopaminergic function, which mediates alcohol-induced reward associated with its abuse liability. Naturally, this has led to the study of serotonergic agents as treatments for alcoholism. SSRIs do not appear to be effective treatment for a heterogeneous alcoholic group. However, they may be useful as treatment for late-onset alcoholics, or alcoholism complicated by comorbid major depression. Buspirone, a serotonin 5-HT(1A) partial agonist, does not appear to be an effective treatment for alcoholics without comorbid disease. Buspirone may, however, have some utility for treating alcoholics with comorbid anxiety disorder. The 5-HT(2) antagonist ritanserin, at pharmacologically relevant clinical doses, does not appear to be an effective treatment for alcoholism. Ondansetron, a 5-HT(3) antagonist ondansetron promises to be more effective for treating alcoholism than either alone. The differential treatment effect of SSRIs and ondansetron among various subtypes of alcoholic is intriguing. Future research is needed to understand more clearly the molecular genetic differences and the interactions of such differences with the environment that typify a particular alcoholic subtype. Such an understanding could enable us to make comfortable predictions as to which alcoholic subtype might respond best to a particular serotonergic agent, which could then be provided.

ADHD

ADHD & New Formulations of Stimulants

New formulations of stimulants for attention-deficit hyperactivity disorder: therapeutic potential.

Authors: Connor DF, Steingard RJ. - Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts 01655, USA. daniel.connor@umassmed.edu
Summary: New formulations of stimulant medications for the treatment of attention-deficit hyperactivity disorder (ADHD) have been an important focus for pharmaceutical industry research.
and development over the past decade. In this article, we review and assess the therapeutic potential of five new stimulant formulations (one immediate release and four longer-acting preparations) that have recently become available for the treatment of ADHD. While the therapeutic potential of immediate-release enantiomers of methylphenidate has not yet been clinically realised, new long-acting formulations of stimulants have changed the standard of care for children, adolescents and adults with ADHD. The longer duration of action of these once-daily compounds, and the consequent expansion of the duration of daily ADHD coverage afforded by them, has introduced the realistic possibility of reducing the overall daily burden of ADHD on affected individuals. 

**Conclusion:** Although more expensive, these new stimulant formulations are easier for patients to use than older stimulants, more resistant to abuse and misuse, and allow for increased privacy of ADHD treatment at school or work.

**Summary:**

**OBJECTIVE:** To examine the relationship between time reproduction, performance variability, and sustained attention deficits in children with attention-deficit/hyperactivity disorder (ADHD) combined (ADHD-C) and inattentive (ADHD-I) subtypes, relative to matched controls. 

**METHOD:** Participants (age range 7.1-14.1 years) performed a time reproduction task. A subset of the ADHD group was also tested on the Sustained Attention to Response Test.

**RESULTS:** First, significantly better performance was observed in matched controls than in children with ADHD on the time reproduction task. Second, there was a significant difference in intraindividual variability scores on the time reproduction, performance variability, and sustained attention performance. Furthermore, these new stimulant formulations are easier for patients to use, more resistant to abuse and misuse, and allow for increased privacy of ADHD treatment at school or work. 

**Conclusions:** Children with ADHD varied more in the size and direction of their time reproduction errors than control children. Those with ADHD-C demonstrated more intraindividual variability than did those with ADHD-I in the size of their errors. This relationship has previously been inferred from common right-lateralized neural circuitry that is thought to subserve these processes.