

and humans their appearance coincides with a receptive endometrium.

Changes in the expression of molecules on the cell surface have also been observed in the conversion of the endometrial surface from a non-receptive to a receptive state. The mucins, a group of antiadhesive molecules, seem to have the most profound effect. They make up part of a thick layer, the glycocalyx, on the luminal epithelial surface of the uterus. In mice the glycocalyx prevents the embryo from direct contact with the endometrium, but changes in concentrations of oestrogen and progesterone after ovulation cause this layer to thin. This exposes the endometrium and enables it to react with the cells of the embryo.⁵ In humans the mucins, specifically MUC-1, are also under hormonal control, but in contrast to mice the endometrial epithelium continues producing MUC-1 while it is receptive to embryo implantation.⁶ This suggests that implantation is different in humans. It is conceivable that a decrease in MUC-1 is localised to specific but as yet unidentified receptor sites in humans and that this decrease is directed by the embryo itself. Alternatively, hormonal changes during the receptive phase may cause a subtle alteration in the structure of MUC-1 that allows the embryo to attach and implant. Furthermore, in both animals and humans the MUC-1 mucin has been found in the fallopian tube. Although it is not known whether it is under hormonal control at this site, it clearly could prevent ectopic pregnancy because of its antiadhesive properties.

Although the regulation of antiadhesion molecules, such as mucin glycoproteins, is undoubtedly important, this alone is not sufficient to support the attachment of the embryo to the uterine epithelial cells. The expression of adhesion molecules, such as integrins, selectins, cadherins, and the immunoglobulin superfamily, is also thought to be involved in the development of a receptive state. In the endometrium, the profile of expressed integrins varies according to the phase of the menstrual cycle; the combined presence of certain integrins has been proposed as a means of distinguishing receptive endometrium from non-receptive.⁷ The pattern of temporal expression of the selectins, cadherins, and immunoglobulin superfamily is less well defined in humans because much of the data are derived from animal studies.

Because of the ethical and moral dilemmas faced by researchers investigating embryo implantation, most of the in vivo data are from studies that have examined the endometrium or embryo in isolation. It is therefore not surprising that the coordination of the process of human embryo attachment has been attributed to oestrogen and progesterone and to "quality embryos."⁸ The embryo is not passive but is an active orchestrator of its attachment and fate. The spatiotemporal expression of embryonic proteins and their influence on the endometrium may prove to be critical. Consequently, co-culture techniques using donor embryos and endometrial epithelial cells with or without their stroma are being developed. Such in vitro approaches will contribute to our understanding of the complex interaction between the embryo and the endometrium. Unravelling the mystery of the mechanisms controlling the receptivity of the human endometrium remains an exciting challenge.

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- Hertig AT, Rock J, Adams EC. A description of 34 human ova within the first 17 days of development. *Am J Anat* 1956;98:425-91.
- Navot D, Scott K, Drosch L, Veeck HC, Liu HC, Rosenwaks Z. The window of embryo transfer and the efficiency of human conception in vitro. *Fertil Steril* 1991;55:114-8.
- Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. *Fertil Steril* 1950;1:3-25.
- Martel D, Malet C, Gautray JP, Psychoyos A. Surface changes of the luminal uterine epithelium during the human menstrual cycle: a scanning electron microscopic study. In: de Brux J, Mortel R, Gautray JP, eds. *The endometrium: hormonal impacts*. New York: Plenum Press, 1981:15.
- Surveyor GA, Gendler SJ, Pemberton L, Das SK, Chakraborty I, Julian J, et al. Expression and steroid hormonal control of Muc-1 in the mouse uterus. *Endocrinology* 1995;136:3639-47.
- Hey NA, Graham RA, Seif MW, Aplin JD. The polymorphic epithelial mucin MUC1 in human endometrium is regulated with maximal expression in the implantation phase. *J Clin Endocrinol Metab* 1994;78:337-42.
- Lessey BA, Ilesanmi AO, Lessey MA, Riben M, Harris JE, Chwalisz K. Luminal and glandular endometrial epithelium express integrins differentially throughout the menstrual cycle: implications for implantation, contraception, and infertility. *Am J Reprod Immunol* 1996;35:195-204.
- Liu HC, Jones GS, Jones HWJ, Rosenwaks Z. Mechanisms and factors of early pregnancy wastage in in-vitro fertilisation embryo transfer patients. *Fertil Steril* 1988;50:95-101.

Treatment of bipolar affective disorder

New drug treatments are emerging, but more clinical evidence is required

Bipolar affective disorder is a common condition which, among mental illnesses, ranks second only to unipolar depression as a cause of worldwide disability.¹ Classically, it manifests itself as repeated periods of illness with complete recovery. However, many patients have a poor outcome: a third suffer chronic symptoms and some 13-24% develop rapid cycling disorder, where four or more episodes occur within a year. The lifetime risk of bipolar disorder is at least 1.2%, with a recognised risk of completed suicide of 15%. Young men, early in the course of their illness, are at highest risk, especially

those with a history of suicide attempts or alcohol abuse and those recently discharged from hospital. Despite its shortcomings, lithium has long been the mainstay of treatment for bipolar affective disorder. Several newer drugs have emerged over the past 10 years, but evidence of their effectiveness remains disappointingly thin.

Ideally, mood stabilisers should treat both mania and depression and prevent their recurrence. Importantly, treatment itself should not precipitate mania or depression or induce rapid cycling. Lithium has been used as a mood stabiliser in bipolar disorder for 50

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years. It continues as a first line treatment in acute episodes and in prophylaxis, but doubts remain about its effectiveness in clinical practice. Some patients respond inadequately to lithium, especially those with rapid cycling disorder and those with mixed mania, where manic and depressive symptoms occur together. Its narrow therapeutic window necessitates frequent blood monitoring, limiting its use in some countries. Lithium discontinuation may precipitate recurrence, a serious problem in the poorly compliant.

The anticonvulsants carbamazepine and valproate are established alternative and adjunctive treatments to lithium. Valproate is the most frequently prescribed mood stabiliser in the United States and is increasingly used in Europe. The mechanism of action of anticonvulsants in bipolar disorder remains unclear. Originally they were used when lithium was poorly tolerated or ineffective; now they are increasingly used as first line monotherapy, yet the evidence for their use remains incomplete. The efficacy of valproate in treating mania was confirmed in the largest placebo controlled trial in which it was studied,² but no randomised controlled trials have examined its effects in bipolar depression. Its use in maintenance treatment has been based on open data and one randomised controlled trial in a group of patients with heterogeneous affective disorders.³ Recently, a randomised controlled trial failed to show that valproate prolonged the time to recurrence of any mood episode over 12 months, although this result is questionable because of the methodological limitations of the study.⁴

The efficacy of carbamazepine in treating mania and bipolar depression and in prophylaxis has been shown in randomised controlled trials, but evidence for its acute efficacy in bipolar depression and overall prophylactic efficacy is not strong. Cochrane reviews on the efficacy of carbamazepine and valproate in bipolar disorder are under way.

All the established mood stabilisers appear to be more effective in treating and preventing mania than depression. Lithium is reported to have specific anti-suicidal effects,⁵ but few data are available on the anti-suicidal effects of carbamazepine and valproate. Although valproate and carbamazepine may be more effective than lithium for mixed states and rapid cycling disorder, much treatment resistance remains. New medications for bipolar depression, mixed states, and rapid cycling disorder are urgently needed: new anticonvulsants and atypical antipsychotics are potential candidates.

The anticonvulsant lamotrigine has been shown to have acute efficacy in bipolar depression in two randomised controlled trials.^{6,7} In the first placebo controlled trial conducted in rapid cycling disorder, lamotrigine improved the overall relapse rate.⁸ Two placebo controlled trials failed to replicate open label evidence of gabapentin's efficacy in hypomania and mania.^{7,9} Cochrane reviews on both these anticonvulsants in bipolar disorder are in progress.

Antipsychotics have long been used in bipolar disorder. Typical antipsychotics are effective in acute mania but may exacerbate postmanic depression. Little evidence supports their prophylactic use, which risks the induction of tardive dyskinesia. Placebo controlled studies of olanzapine and risperidone have shown the acute antimanic efficacy of both these

atypical antipsychotics, although the effects of prolonged use are not yet clear. The prototype atypical antipsychotic, clozapine, is reserved for use in highly refractory cases of bipolar disorder.¹⁰ Intriguingly, ω -3 fatty acids showed mood stabilising effects in one small randomised placebo controlled trial; the underlying mechanism may be the inhibition of signal transduction in neuronal membranes.¹¹

New non-pharmacological treatments such as transcranial magnetic stimulation and vagal nerve stimulation are emerging. Psychological treatments such as cognitive behavioural therapy target recognition of early warning symptoms and compliance with medication and may provide strategies for coping with illness and attendant psychosocial problems.¹²

The management of this common and often debilitating lifelong illness should be shared between primary care and general psychiatrists. Although many new acute treatments for mania have been evaluated in placebo controlled studies over the past 10 years, only a few have undergone evaluation of their prophylactic efficacy in long term randomised controlled trials. Clinicians and their patients need evidence based treatment strategies that produce complete sustained remissions and improve quality of life.

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- Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet* 1997;349:1436-42.
- Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, et al. Efficacy of divalproex versus lithium and placebo in the treatment of mania. The Depakote Mania study group. *JAMA* 1994;271:918-24.
- Lambert PA, Venaud G. Etude comparative du valpromide versus lithium dans la prophylaxie des troubles thymiques. *Nervure* 1992;5:57-65.
- Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, et al. A randomised placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry* 2000;57:481-9.
- Goodwin FK. Anticonvulsant therapy and suicide risk in affective disorders. *J Clin Psychiatry* 1999;60(suppl 2):89-93;111-6.
- Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in out-patients with bipolar I depression. Lamictal 602 study group. *J Clin Psychiatry* 1999;60:79-88.
- Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA, et al. A placebo-controlled evaluation of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacology* (in press).
- Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, et al. A double-blind, placebo-controlled, prophylaxis study of Lamotrigine in rapid cycling bipolar disorder. *J Clin Psychiatry* (in press).
- Pande AC. Combination treatment in bipolar disorder. *Bipolar Disorders* 1999;1(suppl 1):17.
- Calabrese JR, Kimmel SE, Woynshville MJ, Rapport DJ, Faust CJ, Thompson PA, et al. Clozapine in the treatment of treatment-refractory mania. *Am J Psychiatry* 1996;153:759-64.
- Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, et al. Omega-3 fatty acids in bipolar disorder: a preliminary double-blind placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407-12.
- Scott J. Psychotherapy for bipolar disorder. *Br J Psychiatry* 1995;167:581-8.