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Advice in ABC of adolescence is potentially misleading

Editor—Christie and Viner say that delayed puberty in boys can be quite distressing but is almost always a normal variant. They say that boys aged 15 or over with a testicular volume of 4 ml or more can be reassured that puberty is beginning and, by inference, do not require referral to a specialist. This advice is potentially misleading.

For all that it is a variant of normality, constitutional delay in growth and puberty can have adverse psychosocial and sexual consequences.1 2 To deny an apubertal teenager the opportunity to choose low dose androgen treatment until he is into his 16th year would be unusual by present standards. Given the likely ensuing timescale, his doctor might as well refer him straight to an endocrinologist instead of a paediatrician. A testicular volume of 4 ml is well within the range found in boys with irreversible hypogonadotrophic hypogonadism and therefore by no means necessarily indicates that puberty is beginning. Many boys with hypogonadotrophic hypogonadism start puberty but fail to progress beyond the early stages.3 Moreover, a history of cryptorchidism (especially if bilateral) or anosmia should prompt an even earlier referral.4 Neither does a family history of pubertal delay necessarily support a diagnosis of constitutional delay in growth and puberty, given the high prevalence of constitutional delay in growth and puberty among first degree relatives of patients with hypogonadotrophic hypogonadism.5

A recurring theme in the personal stories posted on the www.kallmanns.org website by men with irreversible hypogonadotrophic hypogonadism is of just how difficult it was for them as teenagers to screw up the courage to go to see their family doctor about a lack of secondary sexual characteristics. On being told “not to worry, because it’s just a growth spurt” they then put off seeing a doctor until many years later.

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Competing interests: None declared.

Cognitive behaviour therapy for adolescents with chronic fatigue syndrome

Data are insufficient and conclusion inappropriate

Editor—I have concerns about the design and interpretation of the study reported by Stulmeneijer et al on cognitive behaviour therapy for adolescents with chronic fatigue syndrome.1 The trial arms were not matched for the number of contacts with healthcare professionals. Experience from larger and more carefully controlled randomised interventional trials of patients with chronic fatigue syndrome has clearly shown that short term improvement in symptoms is related directly to the maintenance of regular contacts with healthcare professionals rather than the therapeutic effect of the intervention itself and consequently, the improvement is not sustained once the contacts are stopped.

The authors did not offer patients in their waiting list the opportunity to meet therapists regularly for five months but without having cognitive behaviour therapy. Few follow up data on patients in the intervention arm show that the specific treatment benefit was carried forward without regular contacts with the therapists. A cautious approach is essential in inferring direct benefit from cognitive behaviour therapy in the intervention arm (as opposed to short term benefit from close contact with therapists). The level of activity in some of their participants whom the authors considered to be passive remained unclear.

In their summary points the authors claim that cognitive behaviour therapy was effective by challenging patients’ belief that activity aggravated symptoms. Epidemiological data, however, confirm that fatigue made worse by exercise is a characteristic feature of adolescents at risk of chronic fatigue syndrome.2 Encouraging activity in disabled patients is entirely different from challenging an accepted feature of the disease. A rhetorical approach towards a physically and emotionally challenging condition does not help recovery and only encourages therapeutic failure.

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Competing interests: None declared.

Adolescent development

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increasing in the United States and around the world. In the context of these increases, we are surprised that methods of care that might prevent caesarean delivery have not been pursued more aggressively.

Caesarean delivery is strongly correlated to the age of the mother, parity, and increasing gestational age within the term period of pregnancy.1 If caesarean delivery is an adverse outcome worthy of prevention, if risk factors for caesarean delivery can be identified, and if a latent period exists between the identification of risk and the development of situations requiring caesarean delivery then perhaps a preventive approach—encouraging patients with risk factors to enter labour before their risk can become disease—could lower caesarean delivery rates safely.

Our working group recently described the use of risk driven, prostaglandin assisted induction of labour, and this intervention was associated with a rate of caesarean delivery of only 4%.2 While Declercq et al think that research should be done to elucidate whether the risks of primary caesarean delivery in cases of no indicated risk will be offset by associated benefits, we hope that an equal amount of time and effort will be spent on developing and testing methods that might safely prevent, or lower, rates of caesarean delivery performed for this and the other more traditional indications.

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Early epidurals increase caesarean rate, meta-analysis shows

Editor—The study reported by Mayor in her news item uses the term “neuralaxal analgesia” and claims that early epidurals do not increase the rate of caesarean deliveries.1 This is confusing as the study was not of early epidural anaesthesia, and the oxytocin augmentation rate of 75% at first analysis makes for lack of generalisability.

The claim that women need not worry that early epidurals will lead to increased caesareans is false.1 This trial was about two methods of helping women with pain in early labour. In the so called epidural arm, on their first request for analgesia, women received intrathecal fentanyl, and in the narcotic arm, hydromorphone. On their second request, almost two thirds of women in both arms were 4 cm or more dilated. In the intrathecal “epidural” arm, they received low dose epidurals; in the narcotic arm, hydromorphone.

This trial, as others that have contributed to the Cochrane meta-analysis,1,3 showed no increase in caesareans in the presence of epidural analgesia, but does not acknowledge that most women were in active labour at randomisation, when most will do well. Wong et al, like Sharma et al, the major contributors to the Cochrane meta-analysis,4 have shown only that when women’s pain in the latent phase is managed with intrathecal, narcotic, or other pharmacological or non-pharmacological means, an epidural in the active phase of labour does not increase the rate of caesareans.

The role of an early epidural in contributing to increases in caesarean rates has yet to be studied in an randomised controlled trials, but the sensitivity analysis in the Cochrane meta-analysis, after removing late randomisation studies, shows that early epidurals to more double caesarean rates.

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Competing interests: None declared.

1 Mayor S. Epidurals do not lead to more caesarean sections, study shows. BMJ 2005;330:395-6 (19 February).


Clomipramine and neuroleptic malignant syndrome

Letters

How to prevent caesarean deliveries deserves more study

Editor—Declercq et al bring to light “no indicated risk” as a new classification of caesarean delivery.1 Like other classes of caesarean delivery, annual rates of caesarean sections with no indicated risk have been

Competing interests: None declared.


description of the syndrome includes four primary features: autonomic lability, hyperthermia (pyrexia) without other cause, extrapyramidal syndrome (cog-wheel or lead pipe rigidity), and encephalopathy. Despite superficial clinical similarities between neuroleptic malignant syndrome and serotonin syndrome, they are usually easily differentiated on the basis of careful neurological examination. Neuroleptic malignant syndrome is associated with lead pipe rigidity, bradykinesia, and other extrapyramidal features. Conversely in serotonin syndrome there is hyperkinesia, hyperreflexia, and clonus.

Descriptions of adverse reactions to psychotropic drugs need detailed clinical descriptions of neuromuscular, central, and autonomic features. Using ambiguous or non-specific criteria to label adverse reactions as a particular syndrome while ignoring the pharmacology of the implicated drug may lead to false associations between particular drugs and clinical syndromes and to inappropriate treatment.

Authors’ reply

Editor—Clomipramine is not a neuroleptic and should be regarded as an “antidepressant.” However, as mentioned in our article, this drug has an appreciable blocking effect at dopamine receptor sites, the traditional domain of the neuroleptic drug. This is a weak effect, but it is more potent than several other antidepressant agents. This action is recognised in the current edition of the BNF, which says that neuroleptic malignant syndrome may, very rarely, arise in the course of antidepressant treatment.

In reference to 50 worldwide reports received regarding clomipramine and neuroleptic malignant syndrome or suspected neuroleptic malignant syndrome, in addition to four reports received by the Committee on Safety of Medicines and two published case reports.

We agree that we should have made clear that this patient’s muscle rigidity was of the lead pipe variety, although some widely accepted diagnostic criteria require only severe muscle rigidity. The diagnostic criteria that we tabulated were based on Levinson and Sternbach and referenced in our article. 1,2

We described in this patient an earlier diagnosed episode of serotonin syndrome, and no clinical evidence of rigidity was found on that occasion.

In view of the action at dopamine sites of clomipramine, and the statement in the BNF from the BMA and the Royal Pharmaceutical Society of Great Britain, we would continue to support our diagnosis of neuroleptic malignant syndrome in this informative case.

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Competing interests: None declared.

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3 Neuvonen PJ, Pohjola-Sintonen S, Tacke U, Vuori E. Five cases of postmalignant syndrome and clomipramine, and the statement in the BNF that we tabulated were based on


Risks of gene therapy should be weighed against lack of alternatives for many diseases

Artwork of gene therapy

Editor—Kimmelman provided a comprehensive discussion about the risks and ethics of gene therapy. We certainly cannot predict the future, but the risks should be weighed against the complete lack of alternative options for many of the diseases discussed.

The two cases of T cell leukaemia in the X-linked severe combined immunodeficiency gene therapy trial are presented as typical of the disease type and target cell. For non-lethal disorders such as the inherited retinal dystrophies, minimising risk is of even more importance. However, gene transfer to a post-mitotic cell such as a photoreceptor by using a vector with limited genomic integration, such as recombinant adenovirus, is much less likely to be mutagenic.

The risks of gene therapy must be weighed carefully against the risks and efficacy of existing treatment. Conventional treatments such as organ transplantation, which are no longer considered experimental, are associated with substantial morbidity and mortality. The difficult balance is to steer a path between the ethical application of new untested strategies with the potential to improve health care, and a position of caution. As with conventional medicines, the risks and ethics of gene therapy should probably be reflected in this light.

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Need for expertise based randomised controlled trials

Expertise based design has shortfalls

Editor—Devereaux et al discussed the need for expertise based randomised controlled trials for surgical procedures.1

Secondly, the use of expertise based designs does not necessarily enhance the validity of a surgical trial. Surgical outcome does not depend solely on the operation; other factors that influence the results of an operation are heterogeneous and immeasurable (postoperative management, the surgical team, equipment). A different bias is introduced by the expertise based design, the influence of the overall performance of surgeon A vs B, and in this regard, expertise based design is not necessarily a more valid comparison of operation A vs B.

Moreover, the results of expertise based design trials do not take into account any learning curve that exists when a new operation is introduced. The initial rates of adverse outcomes are higher when a surgeon refines an existing operative technique,2 never mind a new one.

A solution is to perform a randomised trial that has a balanced surgical expertise in
both arms in proportions reflective of the population that will perform the operations. Academics can analyse the “expertise” subgroups, while the rest of us can look at the overall results to determine how an operation will really perform.

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Competing interests: None declared.


Surgical research shares many similarities with psychotherapy research

Editor—Of course the expertise based randomised trial, mooted for surgical procedures by DeVereaux et al., is the norm in psychotherapy research when comparing two different psychotherapies. A similar debate on the interpretation of such trials occurred in the psychotherapy literature.

Research in surgery and psychotherapy share other similarities beyond having to account for practitioner expertise. There is the issue of blindness—hard to achieve for both patient and doctor in these disciplines—as well as the “why test it, it’s obvious it makes a difference” argument. Both disciplines could learn from each other about the design and analysis of clinical research.

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