Antipsychotic-induced hyperprolactinaemia in women: pathophysiology, severity and consequences

Selective literature review

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Background Hyperprolactinaemia has for decades been an inevitable and neglected side-effect of antipsychotic medication. The recent introduction of prolactin-sparing antipsychotic agents makes a re-examination of this problem timely.

Aims To review the literature on antipsychotic-induced hyperprolactinaemia and its consequences.

Method A search was made of the Medline database (1966–2002) for key articles, supplemented by cross-referencing.

Results During antipsychotic treatment prolactin concentrations can rise to ten times normal levels or above, and existing data indicate that 17–78% of female patients have amenorrhoea with or without galactorrhoea. Survey data, however, suggest that clinicians underestimate the prevalence of these conditions. Long-term consequences of antipsychotic-related hypo-oestrogenism require further research but are likely to include premature bone loss.

Conclusions Antipsychotic-induced hyperprolactinaemia should become a focus of interest in the drug treatment of psychiatric patients.

Declaration of interest Both authors have received research grants, lecture fees and conference expenses from the manufacturers of several atypical antipsychotic drugs.

It is thought that the mesolimbic dopaminergic system is pivotal in the control of psychotic symptoms, and in recent years drug development has focused on optimising the effect of antipsychotic agents in this system. The aim was to reduce side-effects caused by antidopaminergic action in non-mesolimbic regions. Most attention has been given to the various movement disorders caused by dopaminergic blockade in the striatum. However, the antidopaminergic effect at the pituitary gland and the resulting increase in prolactin production have been relatively neglected, and clinicians underestimate their prevalence (Hellewell, 1998).

In this article we discuss the physiology of prolactin secretion, the effect of conventional and atypical antipsychotic drugs on circulating prolactin levels, and the consequences of hyperprolactinaemia on endocrine function in women. Since antipsychotic treatment is often initiated when patients are in their late teens or twenties and continued for years or decades, we also consider the possible consequences of prolonged endocrine dysfunction.

PROLACTIN PHYSIOLOGY

Prolactin is secreted in a pulsatile manner by the anterior pituitary gland. There are 13 or 14 peaks per day, with an interpulse interval of about 95 min. The mean pulse amplitude above the preceding nadir is on average about 20–30% of the upper normal value (Veldhuis & Johnson, 1988). Daytime levels and peak amplitudes vary considerably between individuals, and in women levels are higher at the middle and during the second half of the menstrual cycle. Transient and mild increases of prolactin secretion occur in response to meals, stress and sexual activity. The upper limit of unstimulated prolactin levels in men and women varies between laboratories, ranging between 350 mU/l and 550 mU/l. (Serum prolactin concentrations are expressed in mU/l or ng/ml. Because laboratories use different standards the conversion factor varies between these units. In this article we use mU/l because this is more commonly employed in Europe. Other reported values are described in terms of magnitude of change compared with baselines or upper limits of the normal range.)

The main physiological function of prolactin is to cause breast enlargement during pregnancy and milk production during lactation. The reductions in libido and fertility that are associated with nursing may have evolutionary advantages. Prolactin is also involved in promoting maternal behaviour in animals, but whether it is involved in the regulation of this behaviour in humans is not known.

Regulation of prolactin secretion

Hypothalamic dopamine is the predominant prolactin-inhibiting factor. Released into the portal hypophysial circulation it binds to D_2 receptors on the membrane of pituitary lactotroph cells. Stimulation of D_2 receptors has inhibitory effects on prolactin gene transcription, synthesis and release and these effects are mediated in a complex fashion, involving several signal transduction systems. Other substances identified as prolactin-inhibiting factors, for example gonadotrophin-associated protein, gamma-aminobutyric acid (GABA) and acetylcholine, are of uncertain physiological significance in humans.

Serotonin (5-HT) has a stimulatory role in prolactin regulation by mediating nocturnal surges and suckling-induced rises (Tuomisto & Mannisto, 1985). The serotonergic neurons involved project from the dorsal raphe nucleus to the medial basal hypothalamus and exert their effects via 5-HT_{1A} and 5-HT_2 receptor mechanisms. Oestrogens can modulate prolactin secretion in response to reproductive events using various mechanisms. They can inhibit hypothalamic dopamine synthesis, reduce the number of pituitary D_2 receptors, enhance prolactin gene transcription and synthesis and are involved in mitotic activity of lactotrophs (Molitch, 1995). A number of peptide neurotransmitters have prolactin-releasing properties in animals but their physiological role in humans is uncertain.

https://doi.org/10.1192/bjp.182.3.199 Published online by Cambridge University Press

EFFECTS OF PSYCHOTROPIC DRUGS ON PROLACTIN SECRETION

In drug-free patients with acute or chronic major psychiatric disorders prolactin secretory patterns measured throughout the day are no different from those in normal controls (Linkowski *et al*, 1989; Rao *et al*, 1994). An elevation of baseline prolactin levels in medicated psychiatric patients seems therefore to be related to drug effects rather than to the illness itself.

Conventional antipsychotic drugs

All conventional antipsychotic drugs block D_2 receptors on lactotroph cells and thus remove the main inhibitory influence on prolactin secretion. Elevation of prolactin levels occurs within a few hours of treatment initiation (Meltzer & Fang, 1976). Prospective studies with an open or double-blind design have shown that medium-term treatment (3–9 weeks) with therapeutic dosages increases mean baseline prolactin levels up to ten-fold (Meltzer & Fang, 1976; Gruen *et al*, 1978; Oseko *et al*, 1988; Kuruvilla *et al*, 1992; Arvanitis *et al*, 1997; Crawford *et al*, 1997). Low daily dosing regimens (e.g. 200 mg chlorpromazine) can cause significant prolactin elevations (Meltzer & Fang, 1976), and levels have been reported to increase in a dose-dependent manner up to about 600 mg chlorpromazine equivalents (Meltzer *et al*, 1983; Green & Brown, 1988). A partial tolerance may occur during chronic treatment (Brown & Laughren, 1981) although patients treated for several years still have significantly higher baseline prolactin levels than untreated healthy controls (Rivera *et al*, 1976; Zelaschi *et al*, 1996).

Women have significantly greater prolactin elevations than men during chronic antipsychotic treatment with equivalent doses (Wode-Helgodt *et al*, 1977; Kuruvilla *et al*, 1992; Smith *et al*, 2002). In a cross-sectional study of 402 patients (Kinon & Gilmore, 2001) in whom prolactin levels were measured after a minimum of 3 months' treatment with conventional antipsychotics or risperidone, 59% of women and 42% of men had a prolactin level above the upper limit of normal.

When oral antipsychotic therapy is discontinued, baseline prolactin levels may take up to 3 weeks to return to the normal range (Turkington, 1972), depending on the half-life of the drug and its metabolites as well as storage in fatty tissues. In the case of depot medication normalisation may take as long as 6 months (Wistedt *et al*, 1981).

Atypical antipsychotic drugs

'Atypical' antipsychotic drugs are generally defined as agents that cause minimal extrapyramidal symptoms at therapeutic dosages. Seven commercially available drugs are generally regarded as atypicals: clozapine, olanzapine, quetiapine, ziprasidone, risperidone, amisulpride and zotepine. A number of other agents are in development. Clozapine, quetiapine and olanzapine are reported either to cause no increase in prolactin secretion at all or to increase it only transiently and mildly (Meltzer *et al*, 1979; Small *et al*, 1997; Tollefson & Kuntz, 1999). In contrast, risperidone and amisulpride cause a marked and sustained increase in serum prolactin levels.

In a randomised, double-blind, parallel-group study Gruender *et al* (1999) compared treatment with amisulpride (1000 mg daily) and oral flupentixol (25 mg daily) in 32 men and women with schizophrenia who were free of oral antipsychotic medication for at least 4 weeks and depot neuroleptics for at least 3 months. After 4 weeks of treatment mean baseline prolactin levels were significantly elevated in both groups, in the amisulpride group by a factor of 10 and in the flupentixol group by a factor of 5. The difference between amisulpride and flupentixol treatment was significant in the women patients.

Kleinberg *et al* (1999) pooled the data from two large, randomised, double-blind, controlled clinical trials comparing 8 weeks of treatment with fixed daily doses of risperidone (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg and 16 mg), haloperidol (10 mg and 20 mg) and placebo. Prolactin measurements were taken at end-point in 259 women. Levels in the risperidone group were increased above the normal range in proportion to the dose and their mean was significantly higher than in women treated with 10 mg (but not 20 mg) of haloperidol. Whether risperidone has a greater effect on prolactin secretion than equivalent doses of haloperidol, as reported in a small 54-week continuation study (David *et al*, 2000), requires further study.

In another study Breier *et al* (1999) measured prolactin levels in 29 men and women with chronic schizophrenia after a 2-week standardising therapy with oral fluphenazine (20 mg daily) and 6 weeks after switching to clozapine (mean dose 400 mg daily) or risperidone (mean dose 6 mg daily). At the end of fluphenazine treatment prolactin levels were increased by about twice the normal reference range in each group. After switching, levels decreased highly significantly into the normal reference range in the clozapine group, whereas they did not change significantly in the risperidone group.

Preliminary evidence indicates that zotepine can also cause prolactin elevation in humans after both acute and chronic treatment (von Bardeleben *et al*, 1987). Ziprasidone is not yet licensed in the UK but has been introduced in several countries including the USA. Trial data are limited but indicate little effect on prolactin levels (Goodnick *et al*, 2002).

Mode of action

Conventional antipsychotic agents differ in their ability to pass the blood–brain barrier. Because the pituitary gland lies outside this barrier, one would expect that drugs with poor brain penetrability and higher serum concentrations such as sulpiride (Mizuchi *et al*, 1983) would have a greater effect on pituitary prolactin secretion. However, this has not been systematically investigated.

The pharmacological basis of atypical antipsychotic action has been the target of intensive study, and various hypotheses have been put forward. These include a relative limbic selectivity of these agents, a separation of dose and response between pharmacological functions, interactions with neurotransmitter receptors other than D_2, and the binding dynamics at the D_2 receptor (Kapur & Seeman, 2001).

Although 5-HT_2 receptors are involved in the stimulation of prolactin release, this usually occurs only at pharmacological levels of activation (van de Kar, 1991). The effect of antipsychotic agents such as risperidone on prolactin secretion cannot be explained by their action on 5-HT_2 receptors, which is antagonistic and therefore more likely to inhibit prolactin secretion.

Other psychotropic medication

Antidepressants with serotonergic activity, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and some tricyclic antidepressants, can cause modest elevations of prolactin levels (Checkley, 1991; Haddad & Wieck,

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2000). When these drugs are given as monotherapy patients have reported symptoms of hyperprolactinaemia, but such reports are rare (Haddad & Wieck, 2000). In patients whose prolactin secretion is already stimulated by antipsychotic drugs, serotonergic antidepressants have the potential to elevate prolactin levels above the threshold for ovarian dysfunction and galactorrhoea, or to worsen existing symptoms.

CONSEQUENCES OF HYPERPROLACTINAEMIA

Hyperprolactinaemia can cause breast enlargement and galactorrhoea, ovarian dysfunction, infertility, reduced libido, atrophic changes in the urethra and vaginal mucosa, reduced vaginal lubrication and dyspareunia. Acne and mild hirsutism can develop, due to the relative increase of androgenic compared with oestrogenic activity.

Research suggests that individuals vary considerably in their sensitivity to hyperprolactinaemia and in the symptoms which they develop. Of concern also are the potential effects of chronic gonadal underfunction secondary to hyperprolactinaemia. Women with prolonged premenopausal oestrogen deficiency may be deprived of the protective effects of oestrogen on cognitive and cardiovascular function and may have an increased risk of osteoporosis. In addition, chronically elevated prolactin levels may have a number of as yet unknown physical effects. Binding sites for prolactin are widely distributed in the body and several hundred different actions have been described, at least in vertebrate animals (Bole-Feysot *et al*, 1998). Prolactin is a known immunomodulator, for example, and has been linked to tumour growth. However, the clinical significance of these actions has not yet been firmly established.

Several studies have also reported an association of hyperprolactinaemia with hostility, anxiety and depression in women, although the severity of these symptoms appears to be mild (Sobrinho, 1993; Reavley *et al*, 1997).

Effects of hyperprolactinaemia on the hypothalamic–pituitary–ovarian axis

A high prolactin concentration inhibits the activity of the hypothalamic–pituitary–ovarian axis at several levels. It suppresses the pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, inhibits the effect of GnRH on the pituitary gland and blocks the positive feedback effect of oestradiol on luteinising hormone secretion. Women with prolactinoma usually seek medical attention as a result of menstrual disturbances, galactorrhoea or infertility, but not if they are asymptomatic. It is therefore difficult to determine precisely the relationship between prolactin levels and symptom formation.

Five cross-sectional studies investigated menstrual irregularities in women with severe psychiatric illnesses receiving chronic treatment with various conventional antipsychotic agents at therapeutic dosages and found point prevalence rates of 26%, 40%, 45%, 55% and 78% respectively (Polishuk & Kulcsar, 1956; Ghadirian *et al*, 1982; Prentice & Deakin, 1992; Magharious *et al*, 1998; Smith *et al*, 2002). However, these figures need to be interpreted with caution because of the small sample sizes (11–40 patients), an absence of random recruitment and a lack of any clear definition of what constitutes oligo- or amenorrhoea. In data presented by Kleinberg *et al* (1999) only 36 of 451 women with chronic schizophrenia treated with risperidone had a positive rating of amenorrhoea. This low rate (8%) was similar to that seen in the haloperidol and placebo groups. The data are likely to be an underestimate for several reasons: the placebo group consisted of only 14 women, and neither post-menopausal women nor the 20% of women on oral contraceptive medication were excluded. It is also not clear whether the data refer to the prevalence of these symptoms or to the number of new cases compared with the number of cases receiving the antipsychotic medication prior to the treatment trial. The latter method was used in an earlier report for a subgroup of the same study population (Peuskens, 1995). For the two prolactin-raising atypical agents amisulpride and zotepine, there is to our knowledge no published study of sufficient duration that systematically investigates the prevalence or incidence of menstrual irregularities.

Clearly, hyperprolactinaemic symptoms in psychiatric patients treated with antipsychotic drugs are poorly researched. Several key problems are apparent. First, there is a paucity of data, reflecting the low priority given to this phenomenon. Second, many treatment trials simply regard hyperprolactinaemia as a biochemical anomaly and do not comment on whether there were associated symptoms. Third, the short duration of even recent randomised controlled trials (several weeks) means that it is an impossibility to identify amenorrhoea or oligomenorrhoea, as these are usually defined as occurring over a period of at least 3 months. Fourth, the existing cross-sectional studies of women on long-term medication can only identify an association between raised prolactin level and symptoms. Proving a causal relationship requires a follow-up study to determine whether reversal of hyperprolactinaemia is accompanied by symptom resolution. No such systematic study is recorded, but there are case reports of amenorrhoeic women with schizophrenia who resumed menstruation after the antipsychotic medication was discontinued or switched to a prolactin-sparing agent (Beumont *et al*, 1974; Kim *et al*, 1999; Haddad *et al*, 2001).

Other mechanisms

Recent studies have challenged the view that menstrual irregularities in women with schizophrenia are due to drug-induced prolactin elevation alone. In the study by Prentice & Deakin (1992) indicators of illness severity were associated with menstrual dysfunction independently of prolactin levels. In two other studies (Bergemann, 2001; Canuso *et al*, 2002) some women with schizophrenia treated with prolactin-sparing antipsychotic agents also showed evidence of ovarian dysfunction. These findings could indicate either that in some women an organic impairment leads to both the schizophrenic illness and a disturbance in the neuroendocrine regulation of ovarian activity, or that their reproductive function might be affected by other mechanisms, such as stress resulting from the illness or even by an as yet unknown action of antipsychotic drugs on hypothalamic–pituitary function. Irrespective of the mechanisms, the data suggest that the hypothalamic–pituitary system in women with schizophrenia is particularly sensitive to further disturbances such as hyperprolactinaemia.

Effects of hyperprolactinaemia on the breast

In most women who have given birth small amounts of serous fluid can be expressed from one or both breasts despite normal

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prolactin levels. However, significant milk production usually occurs when prolactin levels are above the normal reference range (Peters *et al*, 1986). In women treated with conventional antipsychotic agents spontaneous galactorrhoea of varying severity has been reported to have a prevalence of 10–57% (Wesselmann & Windgassen, 1995). It is more likely to occur in women who have had children and are of premenopausal age (Windgassen *et al*, 1996). The low rate of galactorrhoea in the study by Kleinberg *et al* (1999) – 2.4% in women treated with risperidone and 2.2% in women treated with haloperidol – may be an underestimate for the same reasons as described for the analysis of amenorrhoea. Mammary side-effects of the other two prolactin-raising antipsychotics amisulpride and zotepine have not to our knowledge been systematically studied.

Hyperprolactinaemia and sexual dysfunction

Sexual dysfunction in patients with psychosis is poorly researched, particularly in women, although existing data suggest that it is common and distressing. Ghadirian *et al* (1982) in a sample of 55 out-patients with schizophrenia reported sexual dysfunction in 54% of men and 30% of women. In another study patients rated drug-induced sexual dysfunction as more 'bothersome' than most psychiatric symptoms of their illness (Finn *et al*, 1990). It would be reasonable to expect that this symptom plays a prominent part in determining adherence to medication regimens, although no formal research has addressed this relationship, to the best of our knowledge.

There are several mechanisms by which sexual dysfunction might arise in a person with a psychotic illness. These include the social impact of the illness, the effects of psychiatric symptoms (positive, negative, affective and cognitive), neurotransmitter dysfunction and medication effects. The latter include peripheral and central effects (e.g. sedation, and antidopaminergic, anticholinergic and anti-adrenergic activity) as well as hyperprolactinaemia. The existence of these different mechanisms means that in some people antipsychotic medication might improve sexual functioning compared with the period when they were psychiatrically ill but untreated, but in other people medication might cause a worsening of sexual functioning even if the medication is effective in treating their illness (Barnes & Harvey, 1993).

There is some evidence to support the view that hyperprolactinaemia can cause sexual dysfunction, although the evidence is more consistent for men than for women. Lundberg & Hulter (1991) reported that 68 of 109 women (62%) with hypothalamic–pituitary disorders experienced decreased libido. Among women with hyperprolactinaemia the prevalence was 84% but in those with normal prolactin levels the prevalence was only 32.6% ($P<0.001$). Whether this difference was due to hyperprolactinaemia itself, reduced ovarian hormone production, or both, is not clear.

Effects of hypo-oestrogenism on bone mineral density

Radiologically measured bone mineral density (BMD) is an index of bone mass and is calculated by dividing the mineral content by the area or volume of bone scanned. Techniques commonly used are single or dual-energy X-ray absorptiometry and computed tomographic scanning. Density is at its peak and is relatively constant between the end of growth and the age of about 50 years, and values are normally distributed in women of this age group.

In order to overcome the problems associated with using different types of equipment, results of BMD measurements are usually expressed in units of standard deviations above or below the mean value of young healthy populations (the T-score) or an age-adjusted mean value (the Z-score). For diagnostic purposes two thresholds are used: a T-score of -2.5 or less denotes 'osteoporosis' and a T-score that lies between -1 and -2.49 denotes 'osteopenia'. The BMD value can be used to predict the risk of later fractures and it has been calculated that – at the most vulnerable sites – the risk of fracture approximately doubles with each standard deviation of decrease in age-adjusted mean BMD (Royal College of Physicians, 1999).

In adult life, bone is continually remodelled by resorption and new tissue formation. It has been estimated that in humans as much as 25% of trabecular bone and 3% of cortical bone are resorbed and replaced each year (Parfitt, 1994). Oestrogens have a major role in regulating this process. If oestrogen action is reduced, bone resorption increases relative to new bone formation. This results in loss of tissue and of integrity of the microarchitecture of trabecular bone. Bone becomes more susceptible to stress and may fracture even after trivial trauma.

The oestrogen deficiency associated with the menopause leads to an acceleration in age-related bone loss that can be halted by hormone replacement therapy. A similar process occurs in premenopausal women with hyperprolactinaemic oestrogen deficiency due to hypothalamic lesions or of idiopathic origin. In such patients, radiological studies have shown significant decreases in bone mineral content, ranging from 5% to 25% depending on the site measured (Koppelman *et al* 1984; Schlechte *et al*, 1987). If prolactin levels and menstrual cycles normalise with treatment, BMD values increase but remain significantly lower than those of age-matched normal women (Klibanski & Greenspan, 1986; Schlechte *et al*, 1987).

Psychiatric patients often commence antipsychotic medication in their late teens or early twenties and owing to oestrogen deficiency may not only acquire a reduced peak bone mass but also have a premature acceleration of bone loss. The future lifetime risk of fracture for an average, healthy 50-year-old woman is 13%, 11% and 14% for the three most vulnerable sites – forearm, vertebrae and femoral neck (Royal College of Physicians, 1999). In a female psychiatric patient, if the BMD at the age of 50 years were to be reduced by 1 s.d. her future risk of fracture at these sites might be doubled.

In addition to drug-induced gonadal dysfunction psychiatric patients are exposed to other risks to bone health, particularly excessive nicotine and alcohol consumption, and inadequate dietary calcium and protein intake (Peris *et al*, 1992; Hopper & Seeman, 1994).

Studies of bone density in psychiatric patients

In women exposed to antipsychotic medication bone density has been assessed in two studies. Ataya *et al* (1988) assessed ten premenopausal women who had been treated with antipsychotic drugs for an average of 10 years and had developed amenorrhoea or oligomenorrhoea. Measurements of BMD were taken from the whole spine and the femoral head and neck using dual-photon absorptiometry. Data were compared with age- and gender-related normative values from a large database. Bone density was reduced by about 12%

https://doi.org/10.1192/bjp.182.3.199 Published online by Cambridge University Press

at three sites of the femur, but not in the spine. Although oestradiol levels were not measured, there was a strong positive correlation between bone density and a histological measure of vaginal maturation used as an index of the biological effects of oestrogens. Halbreich *et al* (1995) found significantly reduced BMD values in the lumbar spine in a group of women treated with antipsychotic, antidepressant and mood-stabilising medication, either alone or in combination. However, the contribution of an endocrine dysfunction cannot be interpreted in this study since no information was given on the presence or duration of menstrual cycle disturbances and the duration of psychotropic treatment prior to admission.

In patients with major depression bone mineral densities have been reported to be reduced and it is thought that this is due to hypercortisolism and changes in cytokine activity (see Dinan, 1999). Although depression is common in schizophrenia it is unlikely to contribute to bone loss since it is not associated with alterations in hypothalamic–pituitary–adrenal function in these patients (Rao *et al*, 1995; Ismail *et al*, 1998).

The findings of reduced BMD in patients treated with antipsychotics are preliminary and suffer from small sample sizes and methodological shortcomings. However, they are of concern and need to be followed up in future studies of people with homogeneous diagnoses and psychotropic treatments, and clear histories of prolonged oestrogen deficiency confirmed by hormone measurements.

CLINICAL IMPLICATIONS

- Endocrine symptoms occur in a large proportion of women treated with prolactin-elevating antipsychotic drugs. These symptoms can cause significant distress and may affect compliance with medication.
- A significant proportion of premenopausal women with psychotic disorders may be at risk of premature bone loss and other consequences of chronic hypo-oestrogenism due to long-term antipsychotic medication.
- The presence of menstrual irregularities, breast symptoms and sexual dysfunction should be assessed before and during treatment with prolactin-elevating drugs and management options should be discussed with the patient.

LIMITATIONS

- This article is not a systematic review.
- Estimates of prevalence of clinical symptoms caused by antipsychotic-induced hyperprolactinaemia in women are available only for menstrual irregularities, galactorrhoea and sexual dysfunction, and are based on studies with usually small sample sizes and a cross-sectional design only.
- In women with schizophrenia it is not yet clear how much medication effects other than hyperprolactinaemia and illness-related organic processes contribute to ovarian dysfunction.

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(First received 28 March 2002, final revision 15 August 2002, accepted 3 October 2002)

ACKNOWLEDGEMENT

We thank Professor J. Davis for his helpful comments on the manuscript.

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https://doi.org/10.1192/bjp.182.3.199 Published online by Cambridge University Press