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Title: Setting the boundaries for economic evaluation: investigating time horizon and family effects in the case of postnatal depression

Author: Jemimah Ride

Abstract

Objectives

This study investigates the impact of extending the boundaries of economic evaluation in two dimensions: time horizon and inclusion of family effects. The context is postnatal mental health, where although advocates for investment often include longer-term and family problems in describing the burden of postnatal depression, economic evaluations are usually limited to mothers’ effects with a relatively short time horizon. This discrepancy may lead to suboptimal allocation of healthcare resources.

Methods

The question of whether such boundary extensions could make a difference to decision-making is explored using decision analytic models, populated with data from the literature, to estimate the cost-effectiveness of a hypothetical preventive intervention under alternate boundary-setting approaches.

Results

The results suggest that broader boundaries, particularly extension of the time horizon, could make substantial differences to estimated cost-effectiveness. Inclusion of family effects without extension of the time horizon had little impact, but where a longer time horizon was used, family effects could make a significant difference to the conclusions drawn from cost-effectiveness analysis.

Conclusions

Considerations in applying broader boundaries include the substantial resource requirements for evaluation, potential equity implications, relevance to decision-makers, methods for inclusion, and the interpretation and use of such results in decision-making. However, this context underscores the importance of considering not only caregiving but also family health effects, and illustrates the need for consistency
between the arguments presented to decision-makers and the analytical approach taken in economic evaluation.

Introduction

Although theory recommends that the boundaries of an economic evaluation should incorporate all important differences between the comparators (1), it may not always be obvious where to draw the boundaries; that is, which costs and outcomes to incorporate into a particular evaluation. In a discussion of decision analytic modelling for economic evaluation, Drummond et al. (1) suggest that boundary-setting “should mainly be driven by the extent to which extending the boundaries...is considered likely to impact on the cost-effectiveness of the options being compared” (p.290). Similarly, Gold et al. (2) state that effects which have little impact on the results can safely be excluded from the analysis.

This paper addresses two issues of boundary-setting in the context of postnatal depression (PND): length of time horizon and the inclusion of family effects (quality of life and/or costs of relatives or significant others). Family effects encompass a third boundary: whether a health sector or wider perspective is taken. I outline why these issues are relevant in postnatal mental health, examine the impact of varying each boundary, and explore broader implications.

Maternal PND is a common cause of postnatal morbidity (3, 4), producing a range of distressing and debilitating symptoms (5). Relevant to the choice of time horizon, approximately 30% are still depressed one to two years later (6), and PND is associated with later depression (7). Family effects are pertinent because children whose mothers had PND have higher rates of behavioural, emotional and cognitive problems (8, 9). While factors such as family environment, social support, biology, or adverse life events may explain these associations (10), a causal link is plausible. Children’s development during the postnatal period may be influenced by maternal stress, learned cognitions or behaviours, attachment problems and neurobiological processes (11). A series of reviews found that, after accounting for factors including later
maternal depression, the association between maternal PND and behavioural or emotional problems is ambiguous, but more reliable between PND and cognitive problems (8, 9, 12). These postulated family effects of PND could have significant economic implications. Children’s health costs during the postnatal period are higher when mothers have PND (13). Children with cognitive, behavioural and emotional problems have lower quality of life and higher costs, affecting health, education, social services and justice sectors (14, 15).

Advocates for investment in PND often describe the burden of PND as incorporating mothers’ longer-term depression and children’s problems (16-19), thereby implicitly assuming that intervening in PND could change factors beyond mothers’ postnatal mental health. These broader costs and outcomes would be relevant to economic evaluation if their inclusion would vary the relative cost-effectiveness of comparators. In contrast, economic evaluations of PND interventions are usually limited to mothers’ costs and outcomes with a time horizon of six to eighteen months. This discrepancy may lead to an allocation of healthcare resources that fails to maximise health. Women may be missing out on interventions that would be considered cost-effective if the appropriate boundaries were used, but conversely, if advocates influence decision-making using these arguments in the absence of economic evidence, overinvestment in PND interventions may result, with associated opportunity cost.

Boundary setting for economic evaluation in PND

Following economic theory and the ‘burden of PND’ argument would alter the boundaries of evaluation in three dimensions from the status quo. First, and least controversially, it would entail use of a longer time horizon. Studies show that treatment for depression can improve the risk of recurrence (20) and that preventive approaches can be effective for at least up to two or three years (21).

The second boundary variation would be to include family effects, assuming that some of an intervention’s value lies beyond the patient (22). While there is not yet consensus on how and when to include family
effects in economic evaluations, key decision-makers, including those in the UK and US, have taken the position that relevant family effects should be included (23, 24.). However, they have only been considered in limited contexts, including: prevention of HIV transmission, using a net monetary benefit approach (25); chronic heart failure, by summation of patient and carer quality-adjusted life years (QALYs) (26); children’s vaccinations, taking carer QALYs and productivity losses into account (27-29); and dementia, with patients and carers analysed separately (30). The inclusion of family effects might also affect the appropriate time horizon, since the impact of children’s problems could extend into the child’s adulthood (31).

The third boundary variation, arising from the scope of associated children’s problems, shifts perspective from the health sector to public sector. Family effects relating to caregiving or altruism may only be relevant from a societal perspective (32), but family health effects may be relevant within a health sector perspective, particularly to a nation-wide healthcare payer (such as the UK’s NHS). While some children’s problems affect the health sector, some involve other public sectors, such as education or social services.

If all important differences between comparators should be captured, family effects could be relevant whenever the intervention affects family members’ costs or outcomes (23, 32). PND interventions could modify children’s risks through several pathways. Some could change children’s outcomes even if the association between the outcome and PND is non-causal, such as by targeting family relationships (33) or parenting (34), or through spillover of the intervention by a mother learning and passing on skills to her child. To date, measures of family effects have largely been missing from studies of PND interventions, but the limited evidence suggests that treating PND leads to only slight improvement in child development, if any, even when the mother-child relationship improves (35, 36).

One concern over the inclusion of family effects in economic evaluations is the potential for double counting of health-related quality of life (HRQoL), since the target individual could incorporate the effects on family members’ wellbeing into their own (32). However, family health effects, such as the posited effects of PND on children, are less likely than caregiving effects (37) to result in double counting (32).
Although we lack full data to inform the choice of boundaries for economic evaluation in PND, decisions on funding interventions must still be made. Decision analytic modelling allows synthesis of multiple sources of information and exploration of uncertainty surrounding the decision (38). I explore the potential impact of varying the boundaries for evaluation of PND interventions using alternate versions of a decision analytic model, using the available evidence to inform the methodological decision. The primary issue is not whether the modelled PND intervention is cost-effective, but rather whether altering the boundaries could make a substantial difference to decision-making.

Methods

Decision analytic models mathematically synthesise information regarding the probabilities, costs and outcomes for alternative courses of action (38), and contain structural, methodological and parameter uncertainty (39). Boundary setting could be considered a form of methodological uncertainty (asking which is the “right” approach for decision-making) or structural uncertainty (asking whether all pertinent repercussions are captured). Uncertainty regarding the inclusion of specific effects can be addressed by examining how much they alter the estimated cost-effectiveness (1, 2).

Models populated from the literature were developed to evaluate a hypothetical PND intervention. Each boundary variation was modelled separately, since the purpose was to investigate each independently rather than to estimate an ICER for use in decision-making. The base model captured only mothers’ costs and HRQoL with a time horizon of 12 months, using a decision tree structure, shown in Figure 1, since the time horizon was short (40). This assumes no relevant effects on maternal HRQoL or costs beyond the postnatal period, nor in family members.

[Figure 1 about here]

The first variation added infants’ health sector costs within this 12-month time horizon, assuming that interventions could influence these costs. An extended mothers’ model varied the time horizon up to 11
years (the postnatal period plus 10 years), with Markov components added to the decision tree as shown in Figure 2 (41). This assumed that interventions could affect maternal depression beyond the first 12 months, but that after 11 years there were no relevant differences between control and intervention. Studies following up depression recurrence to 10 years suggest that risk of recurrence diminishes with time (42).

The final variation assumed that prevention of maternal PND could alter children’s risks of later cognitive impairment, even without ongoing effects of the intervention on maternal depression, conceptualising the postnatal period as a key developmental stage in which maternal depression can have lasting effects on children. This model had an extended time horizon of up to 11 years, covering primary school age for children, as shown in Figure 3. The various model specifications are outlined in Table 1.

The models were developed using TreeAge Pro 2015 software. The population of interest was postnatal women and their children in the UK, since much of the data came from that setting; this gave an explicit societal threshold of £20,000-30,000 per QALY for cost-effectiveness analysis in healthcare (23). A health sector perspective was taken, except for the children’s model, which expanded to a public sector perspective to accommodate educational costs. A discount rate of 3.5% was applied to costs and QALYs (23), with discounting applied back to the child’s birth. All costs were converted to 2014 pounds sterling using OECD purchasing power parities (at which time £1.00=US$1.32) (43) and consumer price inflation data (44). Table 2 details the model parameters and their sources, taken from meta-analyses and systematic reviews where available, otherwise from the best quality available study data. The longest time horizon was 11 years, based on long-term follow up studies of PND and due to scarcity of data beyond this point.

The diversity of parameter inputs required multiple sources of data and certain assumptions. Rates of comorbidity between cognitive, behavioural and emotional problems in children of women with PND were unavailable, and it would not be safe to assume that these are independent risks (45). The children’s model was therefore restricted to cognitive impairment as this demonstrates the most consistent association with mothers’ PND (8, 9, 12). Model inputs were HRQoL for children with and without cognitive impairment at
age 11 (14), the additional risk of having special educational needs at the same age, conditional on maternal PND (46) and the excess costs associated with special education needs (47). The label “special educational needs” in the indicates some form of learning difficulty requiring additional resourcing (47). No cost or HRQoL impact of cognitive impairment entered the model until school age (five years).

A preventive intervention was modelled to avoid the need to make assumptions about the impact of therapeutic interventions on children and particularly the mechanisms behind such impact, such as a reduced duration of exposure to depression and the timing of this exposure. The hypothetical intervention was intended to be sufficiently realistic without signifying any particular intervention. It modified only the risk of PND within the first two months, with subsequent events conditional upon this. The PND risk reduction was based on a meta-analysis of psychological and psychosocial interventions, which found the average risk reduction to be 7-34% (33). The control arm represented treatment as usual. As implied by the ‘burden of PND’ argument, it was assumed that successful prevention of PND had consequent benefits for children.

One-way sensitivity analysis tested discount rates between 5% and zero. Combined parameter uncertainty was estimated using probabilistic sensitivity analysis, with 1,000 Monte Carlo simulations, to estimate the probability of cost-effectiveness at the NICE threshold of £20,000-30,000. The key result was the change in the estimated incremental cost-effectiveness ratio (ICER) between base and extended models.

No specific funding was received to support this work. This paper is based on work using publicly available data. No ethics committee has reviewed this paper as there were no relevant ethical issues.

Results

The base model, which included only mothers’ effects in the first postnatal year, found the hypothetical preventive intervention to be not cost-effective (estimated ICER approximately £70,000/QALY). Figure 4 displays the impact of the boundary variations on the intervention’s estimated cost-effectiveness. The first
variation, adding infant postnatal healthcare costs to the base model, resulted in an estimated ICER of just under £68,000/QALY. Extending the time horizon for mothers’ effects made a substantial difference, dropping the estimated ICER below the upper bound of the NICE threshold (£30,000/QALY) after the time horizon reached 3 years.

[Figure 4 about here]

The extended children’s model with a health sector perspective added children’s health costs in the first year, plus children’s HRQoL during the primary school years (5 to 11 years). This model estimated the ICER to be £39,000/QALY at a time horizon of 11 years. Taking a public sector perspective included children’s education sector costs and HRQoL during the primary school years. Under these specifications, the ICER dropped below the upper threshold at a time horizon of 10 years.

One-way and probabilistic sensitivity analyses did not greatly alter the findings (see supplementary Table 1). Varying the discount rate in one-way sensitivity analysis between a rate of 5% and no discounting made only slight differences to conclusions drawn about any of the boundary variations. The probability of cost effectiveness at the NICE threshold was, at most, approximately 50%, due to the considerable combined parameter uncertainty, even when a boundary variation had substantial effects on the point estimate of the ICER.

Discussion

These results suggest that setting the boundaries in line with advocacy arguments and economic theory could make a substantial difference to economic evaluation in PND. Of the extensions tested, the longer time horizon for mothers’ effects resulted in the largest reductions in the estimated ICER, was the least controversial methodologically, and required the least heroic assumptions regarding the effects of PND interventions. If developing PND expresses an underlying predisposition to depression that may be triggered by various life events, some preventive interventions (such as enhanced support) might not
change the woman’s later risk. However, interventions which better equip women to cope with such life events might have ongoing benefit. At least, the results suggest merit in exploring whether potentially cost-effective preventive interventions may be being overlooked due to the use of relatively short time horizons.

The children’s problems associated with PND and their substantial cost and HRQoL consequences might be quite persuasive in arguing for increased investment in PND. However, this study makes clear how much these arguments rely on assumptions regarding the effect of PND interventions on these broader risks, which are as yet largely unsupported in the literature.

Without extending the time horizon, the inclusion of children’s effects had little effect on the estimated cost-effectiveness of the intervention, so that for similar interventions, inclusion of family effects might not make a difference to decision-making if the time horizon is short. The impact of including children’s later effects was limited by scarcity of data, but did show a substantial effect with the longer time horizon, despite the restrictive assumptions. This model only included one of the postulated effects of PND on children; examining the full range of children’s outcomes when evaluating PND interventions could be important for decision-making. The third boundary extension, broadening the perspective to include education sector costs, might be inappropriate where the focus is health sector decision-making, but could be relevant where such effects are considered by decision-makers as part of the ‘burden of PND’ argument. The constraints in modelling children’s effects indicate the need for more decisive evidence on these points.

Because of simplifying assumptions in construction of the models the results should be interpreted with caution. The use of separate extended models meant that the joint uncertainty surrounding mothers’ and children’s effects was not estimable. It would be unsafe to assume that the results from each model could be combined by simple addition. For simplicity, the models did not include as outcomes either suicide related to depression or death due to other causes, as these are rare events in this population (48, 49). The use of cohort models did not allow for individual heterogeneity, such as past history of mental illness or severity of depression, to vary response to the intervention and or downstream risk.
The analysis relied on one strong assumption: that preventing maternal PND would neutralise the risks usually associated with PND, both for mothers and children. Although other pathways of association are likely to contribute, this strong assumption was consistent with the ‘burden of PND’ argument. Spillover of intervention effect (such as a mother passing on psychological skills to her child) was not modelled explicitly, but might contribute to this lowering of risk for children. In some women depression starts during pregnancy, and some interventions address risk during this period, so the analysis could be extended to include pregnancy, an additional period of potential influence on children’s development.

This analysis has highlighted a lack of evidence regarding family effects of PND interventions. Al · Janabi, Van Exel (27) suggest approaches to this data problem, including the collection of family data in trials of interventions. PND in fathers is more than twice as likely when the mother had PND (50). It would therefore be relevant to collect data on partners as well as children of women with PND in trials of both preventive and therapeutic interventions. This could inform the joint modelling of mothers’ and family members’ longer-term effects.

An open question is how family effects might best be incorporated into economic evaluation. A single estimate incorporating mothers’ and family effects would be needed for decision-making. These results are a first, preliminary examination of the impact of including family effects in PND evaluations, but indicate that such methodological work could be warranted. Bobinac et al. (51) suggest that presenting a combined result may be appropriate if each person’s outcome is measured using the same instrument. Al-Janabi et al. (52) propose applying multipliers to the standard ICER formula to account for family health effects. The joint analysis of patients’ and children’s costs and outcomes might be simpler within a cost-benefit framework. However, since many high-income countries (including the UK) focus on maximising health within the constraints of a budget rather than maximising individuals’ utility (53), cost-effectiveness analysis might better fit the needs of decision-makers.

Many discussions of family effects address conditions affecting older adults (such as dementia) or children, rather than child-rearing adults, and portray family effects as mediated through caregiving or distress (51), not necessarily representing HRQoL (32). However, the mechanisms by which a mother’s mental health
could affect her child are qualitatively different (11) and could require a different conceptualisation, relevant even within a health sector perspective. Family HRQoL might be particularly important for mental health interventions, being worse in families of someone with a mental illness, even after accounting for other health and sociodemographic factors (54). Larger decrements in family members’ subjective wellbeing are associated with mental health than physical health problems (37), suggesting that the impact on families from intervening in mental health might differ from the average family impact of interventions within the healthcare system (52).

A longer time horizon dictates a greater role for discounting, and more resource expenditure on gathering costs and outcomes. The inclusion of family effects would also demand more data on the effects of interventions on family risks, costs and HRQoL. Both extensions could require more complex models and introduce greater uncertainty around the results.

Inclusion of family effects could appear to give higher priority to depressed women with children than those without children, since society is seen as getting better value for money from investing in mothers. Societies may be willing to prioritise those with dependents (55, 56). If family effects are only relevant in some areas, another consideration is how to compare an ICER incorporating family effects to an ICER based on individuals. Al-Janabi, van Exel (52) apply multipliers to both to the incremental effects of the intervention and to the threshold value for cost-effectiveness to account for average family effects displaced by new investment. To avoid misleading comparisons and allow decision-makers to use their own judgement regarding potential equity implications, family effects may fit best in supplementary rather than main analysis (32).

Concluding remarks

Postnatal mental health provides a novel context in which to discuss boundary setting for economic evaluation. It highlights the importance of using an appropriate time horizon and of considering family health effects, particularly for mental health problems and/or where the patient may be a parent of dependent children. It also illustrates the need for consistency between the arguments presented to decision-
makers and the analytical approach taken in economic evaluation. The uncertainty surrounding these results indicates that similar uncertainty might surround existing decisions on investment in PND interventions.

This first exploration of boundary setting in economic evaluation of PND interventions provides support for further endeavours to test and incorporate broader boundaries. The results encourage the use of a longer time horizon for mothers’ effects, whilst additional data and methodological work are needed to inform the inclusion of family effects. However, effectively ignoring these broader sets of costs and outcomes may mean that resources in postnatal mental health are misallocated, and that some women are not benefitting as they could from interventions which might be cost-effective.
43. OECD. Purchasing power parities for GDP. Organisation for economic co-operation and development, 2015.
Table 1. Alternate boundary setting approaches modelled

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Mothers</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRQoL</td>
<td>Costs</td>
</tr>
<tr>
<td>Base model</td>
<td>Year 1</td>
<td>Year 1 (health)</td>
</tr>
<tr>
<td>Base model with infant costs</td>
<td>Year 1</td>
<td>Year 1 (health)</td>
</tr>
<tr>
<td>Extended mothers’ model</td>
<td>Years 1 - 11</td>
<td>Years 1–11 (health)</td>
</tr>
<tr>
<td>Children’s model – health sector*</td>
<td>Year 1</td>
<td>Year 1 (health)</td>
</tr>
<tr>
<td>Children’s model – public sector*</td>
<td>Year 1</td>
<td>Year 1 (health)</td>
</tr>
</tbody>
</table>

*In the children’s model, mothers’ effects are only included in the first year, as in the base model.

†Impact of cognitive disorders does not appear in the model until school age.

‡Infant costs dependent on mother’s PND status only available for the first year.
Table 2. Model inputs & their sources in the literature

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PND</th>
<th>No PND</th>
<th>Distribution</th>
<th>Derived from</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probability parameters – decision tree</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal PND (from birth to 3 months)</td>
<td>0.13</td>
<td></td>
<td>Beta</td>
<td>O'Hara and Swain (3)</td>
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<td>Maternal depression at 12 months</td>
<td>0.31</td>
<td>0.07</td>
<td>Beta</td>
<td>Beeghly, Weinberg (57)</td>
</tr>
<tr>
<td><strong>6 month transition probabilities – Markov components, extended mothers’ models</strong></td>
<td></td>
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<tr>
<td>Depression to remission (time-dependent)</td>
<td>0.54 in 1st 6mo – 0.09 after 5 years</td>
<td>Beta</td>
<td>Keller, Lavori (58)</td>
<td></td>
</tr>
<tr>
<td>1st recurrence of depression after PND (time-dependent)</td>
<td>0.13 in 1st year – 0.02 after 12 years</td>
<td>Beta</td>
<td>Solomon, Keller (42)</td>
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<tr>
<td>2nd recurrence of depression after PND (time-dependent)</td>
<td>0.23 in 1st year – 0.07 after 5 years</td>
<td>Beta</td>
<td>Solomon, Keller (42)</td>
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<td>1st depression in females 25-34yo</td>
<td>0.005</td>
<td></td>
<td>Beta</td>
<td>Kessler, Mcgonagle (59)</td>
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<td><strong>Transition probability at 5 years for children’s model</strong></td>
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<td>Child special educational needs</td>
<td>0.46</td>
<td>0.25</td>
<td>Beta</td>
<td>Hay, Pawlby (60)</td>
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<td><strong>HRQoL parameters – mothers’ models</strong></td>
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<td>Depression during postnatal period</td>
<td>0.696</td>
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<td>Petrou, Morrell (61)</td>
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<td>Non-depressed during postnatal period</td>
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<td>Revicki and Wood (62)</td>
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<td>Ara and Brazier (63)</td>
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<td><strong>HRQoL parameters – children’s model</strong></td>
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<td>Petrou, Johnson (14)</td>
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<td>983</td>
<td>Gamma</td>
<td>Petrou, Cooper (13)</td>
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<tr>
<td>Infant, postnatal</td>
<td>888</td>
<td>860</td>
<td>Gamma</td>
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<td>Excess cost per case of depression</td>
<td>203</td>
<td></td>
<td>Gamma</td>
<td>Thomas and Morris (64)</td>
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<td><strong>Cost parameters – education sector (annual)</strong></td>
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<td>Special educational needs, primary</td>
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<td></td>
<td>Gamma</td>
<td>Boyle, Burton (65)</td>
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<td>Uniform</td>
<td>Woolhouse, Brown (67)</td>
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*Costs expressed in in 2014 £
Figure 1. Format of the base model
Figure 2. Format of Markov components in mothers’ extended model
Figure 3. Extensions in the children’s model
Figure 4. Impact of boundary changes on estimated ICER.

ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year