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MINI REVIEW ***Developments in Reproductive Biology and Medicine***

Elagolix for endometriosis: all that glitters is not gold

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ABSTRACT: Elagolix, an orally active non-peptidic GnRH antagonist, has been approved by the Food and Drug Administration for the management of moderate to severe pain associated with endometriosis. As the degree of ovarian suppression obtained with elagolix is dose-dependent, pain relief may be achieved by modulating the level of hypo-oestrogenism while limiting side effects. Elagolix may thus be considered a novelty in terms of its endocrine and pharmacological properties but not for its impact on the pathogenic mechanisms of endometriosis, as the target of this new drug is, yet again, alteration of the hormonal milieu. Given the oestrogen-dependent nature of endometriosis, a reduction of side effects may imply a proportionate decrease in pain relief. Furthermore, if low elagolix doses are used, ovulation is not consistently inhibited, and patients should use non-hormonal contraceptive systems and perform serial urine pregnancy tests to rule out unplanned conception during periods of treatment-induced amenorrhoea. If high elagolix doses are used to control severe pain for long periods of time, add-back therapies should be added, similar to that prescribed when using GnRH agonists. To date, the efficacy of elagolix has only been demonstrated in placebo-controlled explanatory trials. Pragmatic trials comparing elagolix with low-dose hormonal contraceptives and progestogens should be planned to verify the magnitude of the incremental benefit, if any, of this GnRH antagonist over currently used standard treatments. The price of elagolix may impact on patient adherence and, hence, on clinical effectiveness. In the USA, the manufacturer AbbVie Inc. priced elagolix (Orilissa™) at around $10 000 a year, i.e. $845 per month. When faced with unaffordable treatments, some patients may choose to forego care. If national healthcare systems are funded by the tax payer, the approval and the use of a new costly drug to treat a chronic condition, such as endometriosis, means that some finite financial resources will be diverted from other areas, or that similar patients will not receive the same level of care. Thus, defining the overall 'value' of a new drug for endometriosis also has ethical implications, and trade-offs between health outcomes and costs should be carefully weighed up.

Key words: endometriosis / pelvic pain / medical therapy / GnRH agonists / GnRH antagonists / oral contraceptives / progestogens

Introduction: the rise of a wonder drug

On 24 July 2018, the Food and Drug Administration approved elagolix, an orally active non-peptidic GnRH antagonist, for the management of moderate to severe pain associated with endometriosis. Despite enthusiastic announcements regarding this new potential blockbuster drug (Bradley, 2017; Dun and Taylor, 2017) named Orilissa™, it is currently not clear whether the marketing of elagolix will translate into major benefits for women with endometriosis.

[†]A complete list of group members can be found in the Appendix.

Impact of elagolix on endometriosis: 'the song remains the same'*

(*Led Zeppelin. Warner Bros., USA, 1976)

Antagonistic analogues of GnRH compete with the endogenous decapeptide by binding GnRH receptors in the anterior pituitary, but without inducing their activation (Hornstein, 2017). Contrary to GnRH agonists, antagonists do not provoke the initial gonadotropin release, also known as flare-up phase. Elagolix has a non-peptide structure, does not undergo gastrointestinal proteolysis, can be given orally and suppresses ovarian function in a dose-dependent manner (Struthers *et al.*, 2009; Melis *et al.*, 2016; Ng *et al.*, 2017). This allows modulation of oestradiol levels, thus, potentially providing relief of endometriosis-associated pain and a reduction in the side effects caused by the extreme hypo-oestrogenism induced by GnRH agonists (Diamond *et al.*, 2014; Dun and Taylor, 2017).

Elagolix may be considered a novelty in terms of its endocrine and pharmacological properties but not in terms of its impact on the pathogenic mechanisms of endometriosis. In fact, the target of this new drug is, yet again, modification of the hormonal milieu (Guo and Groothuis, 2018). This can be achieved also by using combined hormonal contraceptives (CHC), progestogens, androgens (e.g. danazol) or GnRH agonists. However, despite the different impact on the metabolic activity of ectopic endometrial cells, no drug actually eliminates them. Hormonal modulation, however induced, may control endometriosis but not cure it (Vercellini *et al.*, 2011).

From this perspective, the purported advantages of elagolix over GnRH agonists appear unclear (Guo and Groothuis, 2018). Firstly, modifying the level of hypo-oestrogenism may imply concurrent but inverse effects on pain and side effects, i.e. a reduction in side effects may come at the price of reduced pain relief. Secondly, elagolix does not consistently inhibit ovulation, especially at low doses (Struthers *et al.*, 2009; Ng *et al.*, 2017). Patients should therefore use non-hormonal contraceptive systems during treatment and perform serial urine pregnancy tests to rule out unplanned conception in the presence of amenorrhoea. Thirdly, with regard to the initial gonadotropin surge with GnRH agonists, injecting depot GnRH agonists during the mid-luteal phase, or using an oral progestogen for the first 7–10 days after the first injection, usually prevents the flare-up phase (Vercellini *et al.*, 2018a). Finally, the preference for daily oral or depot intramuscular or subcutaneous use is subjective.

The investigator's and industry's point of view: efficacy: can elagolix work?

The short- and medium-term results of large phase III explanatory trials on the effect of elagolix for the treatment of endometriosis were recently published (Taylor *et al.*, 2017; Surrey *et al.*, 2018). Two oral daily doses (150 and 400 mg) were tested against a placebo in the first two multi-centre trials (Taylor *et al.*, 2017). At the 3-month evaluation, the proportions of responders, in terms of dysmenorrhoea relief, were 43–46% and 72–76% in the lower- and the higher-dose elagolix group, respectively, compared with 20–23% in the placebo group. With respect to non-menstrual pelvic pain, the differences were smaller, as the proportions of women who had a clinical response were 50% and 55–58% in the lower- and the higher-dose elagolix group, respectively, compared with 37% in the placebo group. Hot flushes were reported by slightly less than half of women using the higher elagolix dose. In the same group, the mean percent bone mineral density (BMD) reduction at the lumbar spine observed at the 6-month follow-up varied from −2.49 to −2.61. Despite the use of two forms of non-hormonal contraception (e.g. condom plus spermicide), some women using elagolix conceived.

The 12-month data of those women who were randomized to elagolix in the above two trials and who agreed to use the drug for another 6-month period, are also available (Surrey *et al.*, 2018). Of note, 952 women were originally allocated to the two elagolix groups (150 and 400 mg/day) but only 569 were recruited for the two extension studies, as many participants did not complete the first 6 months of treatment or refused to prolong it for another 6 months. Therefore, most participants with the worst prognosis (i.e. those who did not respond to, or did not tolerate, elagolix) were excluded. As 111 participants prematurely discontinued the extension studies, less than half the women originally recruited completed the 12-month treatment period (458/952 = 48%). Responder rates for dysmenorrhoea and non-menstrual pain were only slightly improved compared with those observed at the 6-month follow-up. The proportion of responders with dyspareunia was 45–46% in 150 mg/day users, and 58–60% in 400 mg/day users. The mean percent change from baseline in lumbar spine BMD was −3.60 to −3.91% for the 400 mg/day group.

In summary, the effect of low-dose elagolix was small and not associated with a statistically significant reduction in the use of rescue analgesics including opioids. The effect of high-dose elagolix was greater in terms of pain reduction but, as expected, associated with a higher incidence of hypo-oestrogenic side effects and with a more severe degree of bone demineralization.

The clinician's point of view: effectiveness: does elagolix work in practice?

The above trials assessed whether elagolix does more good than harm under ideal circumstances (Haynes, 1999). Explanatory trials are conducted on a selected patient population that will probably benefit most from the use of the drug under study (e.g. women who previously did not respond to progestogens and GnRH agonists were excluded) and that is at low risk of important untoward effects (e.g. patients who had a *Z*-score ≤ −1.5 at screening with dual-energy x-ray absorptiometry scan of the lumbar spine, femoral neck or total hip BMD were excluded). No specific information was provided on participants with deep endometriotic lesions, who have a notoriously worse prognosis (Vercellini *et al.*, 2016a, 2017). In the type of trial published, patients receive special attention from highly motivated physicians and nurses, do not pay for the drug being studied nor the repeated blood tests, examinations or diagnostic imaging and follow a carefully pre-planned research protocol. In these circumstances, participants are most likely to adhere and respond to the experimental treatment (Rothwell, 2005; Guo, 2014; Nijjar *et al.*, 2017).

Industry would probably like us to believe that these findings, obtained under particularly favourable circumstances, can be replicated in everyday practice. However, the real world is usually rather different. Unselected women, with varying histories, lesion types and co-morbidities, access care after being on a waiting list for an unpredictable amount of time, pay for tests and treatments, and are looked after by physicians and staff working under time constraints (Haynes, 1999).

We should also query whether elagolix provides distinct advantages over currently used treatments (Perricos and Wenzl, 2017). Hornstein (2017) stated 'since the trials did not include an active comparator, it is unclear how the benefits and harms of elagolix compare with currently available medications'. This is precisely what patients need to know to make informed choices. According to guidelines issued by major gynaecological professional associations, the standard first-line treatments for symptomatic endometriosis are low-dose CHC and progestogens (Dunselman *et al.*, 2014; Practice Committee of the American Society for Reproductive Medicine, 2014; National Institute for Health and Care Excellence, 2017). Consequently, pragmatic trials should be carried out to assess the actual incremental benefit, if any, of elagolix over CHC or progestogens chosen as active comparators.

It should be noted that elagolix (150 mg/day) has only been assessed against an active comparator (depot three-monthly 104 mg subcutaneous medroxyprogesterone acetate, DMPA) once in a phase II, multicentre RCT (Carr *et al.*, 2014). The effect of the GnRH antagonist was similar (not inferior) to that of cheap DMPA in terms of BMD variation and pain symptom reduction. Three unplanned pregnancies (3/168 = 1.8%) were observed in the elagolix group.

The healthcare policymaker's point of view: efficiency: is elagolix worth it?

Healthcare decision makers will need to know whether elagolix is worth the resources it requires. The price of elagolix is therefore crucial in determining its cost-effectiveness. If elagolix is marketed in Europe, the European Medicine Agency will have to determine not only its price but also the opportunity costs of this new GnRH antagonist, especially, for instance, in the case of years of treatment. In countries with national healthcare systems funded by the tax payer, the approval and use of a new costly drug to treat a chronic condition such as endometriosis, means that some finite financial resources will be diverted from other areas, or that similar patients will not receive the same level of care (Vercellini *et al.*, 2018b, 2018c). Thus, assessing the 'value' of a new drug for endometriosis also has ethical implications.

Decisions should be based on the difference in effect size with respect to safe and well tolerated low-dose CHC and progestogens. Costs must not be excluded in this assessment, otherwise the value of any medical intervention would be identical to clinical effectiveness (Pandya, 2018). Reducing low-value healthcare is a priority in endometriosis management (Vercellini *et al.*, 2015), and careful weighing up of trade-offs between health outcomes and costs is required. According to Pandya (2018), cost-effectiveness analyses 'can be used to identify low-value healthcare services that improve the health of patients but are not worth the additional costs required to achieve these healthcare gains'. In other words, the definition of low-value healthcare should not be limited to interventions that do more harm than good, but should also include those interventions that offer some limited benefits but at the price of excessive opportunity costs that prevent better investment of resources in other cost-effective healthcare services. Price will thus determine whether Orilissa™ can be considered a high- or low-value medical treatment.

In the USA, the manufacturer AbbVie Inc. priced elagolix (Orilissa™) at around $10 000 a year, i.e. $844.87 per month. According to Thomson Reuters, AbbVie expects the drug to become a multibillion-dollar product, generating $1 billion to $2 billion a year just from endometriosis. (https://www.reuters.com/article/us-abbvie-orilissa/abbvie-prices-new-endometriosis-drug-at-10000-a-year-idUSKBN1KE2O3; accessed on 9 August 2018).

On 3 August 2018, the Institute for Clinical and Economic Review (ICER) released a final evidence report on elagolix for the management of endometriosis. According to this report, 'the evidence was not adequate to determine whether elagolix offers a net health benefit compared to no treatment'. Moreover, 'the evidence was not adequate to distinguish the net health benefit of elagolix from that of treatment with either a GnRH agonist (leuprorelin acetate) or a hormonal contraceptive (depot medroxyprogesterone), due to limited and mixed evidence on clinical effectiveness and potential risks'. The ICER is going to issue an Affordability and Access Alert for elagolix, as 'at current prices, only about one-quarter of eligible patients, for whom clinical experts believe elagolix would be considered, could be treated before the budget impact would cross ICER's threshold of a net addition of over $915 million per year over 5 years' (https://icer-review.org/announcements/elagolix-final-report/; accessed on 9 August 2018).

According to Taylor *et al.* (2017) 'long-term or repeated courses of elagolix are likely to be needed for medical management'. In this case, especially if used at 400 mg/day (i.e. the more effective dose), elagolix will need to be combined with some form of add-back therapy. Indeed, almost 1600 patients are currently being recruited in two multi-centre, phase III studies to evaluate the safety and efficacy of elagolix in combination with oestradiol/NETA for moderate to severe pain associated with endometriosis (https://clinicaltrials.gov/ct2/show/NCT03213457?term=elagolix&cond=Endometriosis&rank=2;

https://clinicaltrials.gov/ct2/show/NCT03343067?term=elagolix&cond=Endometriosis&rank=6; accessed on 25 August 2018).

The woman's point of view: patient preference and affordability of care

How should healthcare providers inform patients with endometriosis who prefer medical therapy to surgery about the use of elagolix? They cannot assert that this new drug provides more effective pain relief than existing medications, or that it impacts more on the natural course of the disease, nor can they affirm that it is more tolerable or associated with fewer side effects, simply because no comparative studies are available. They should also explain why it would be better to use elagolix instead of CHC, which have been demonstrated to relieve endometriosis-associated pain and improve patient quality of life (Jensen *et al.*, 2018; Vercellini, 2018), or progestogens, which have

been indicated as the first-line treatment of choice based on endocrine and metabolic considerations (Casper, 2017).

What they must tell them is that Orilissa™ is frequently associated with hot flushes, headache and nausea (Taylor et al., 2017; Surrey et al., 2018), does not consistently suppress ovulation (Struthers et al., 2009; Ng et al., 2017), and, as opposed to CHC and some progestogens, does not provide reliable contraception (Taylor et al., 2017; Surrey et al., 2018). Therefore, in addition to using non-hormonal

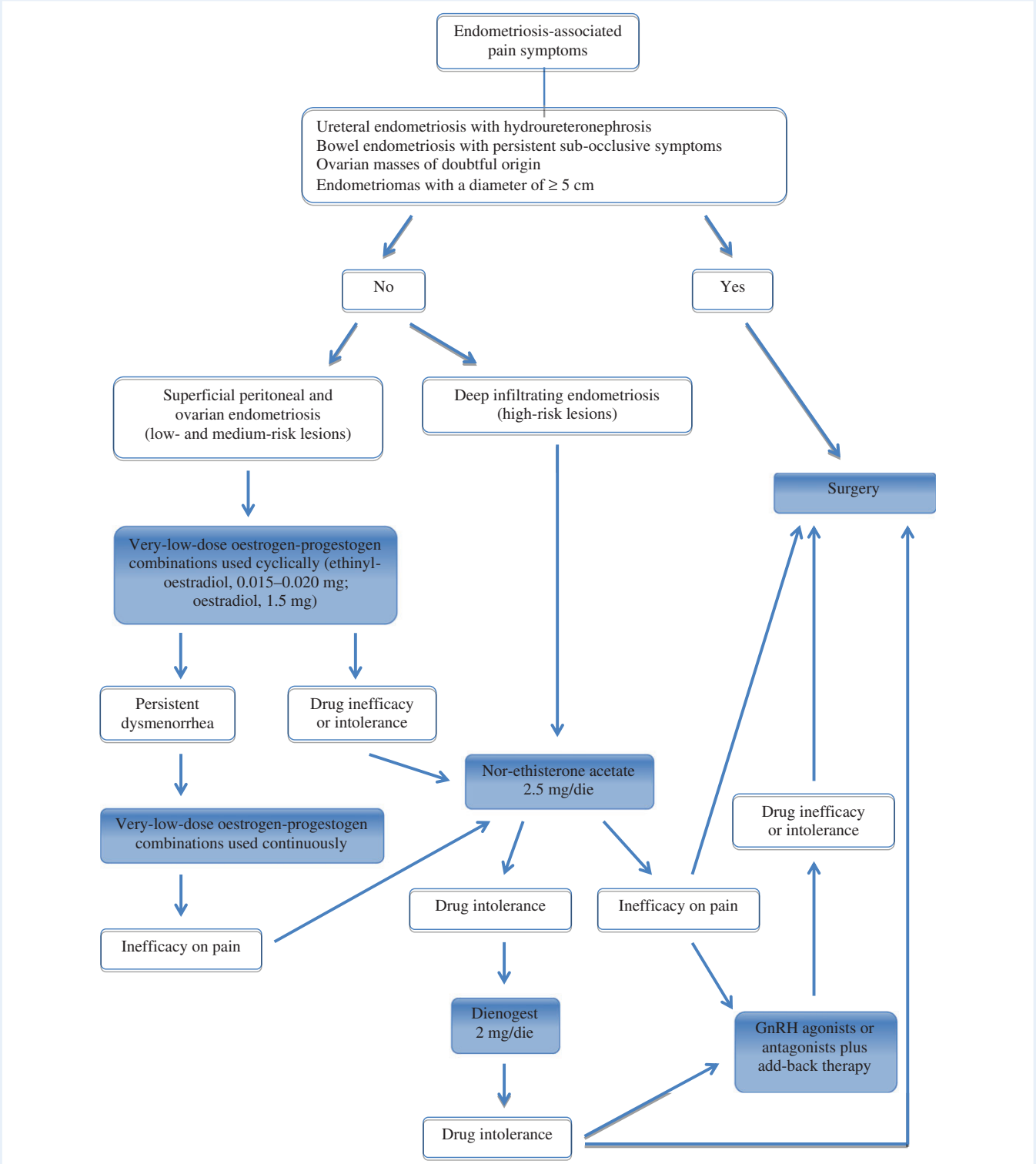

Figure 1 Suggested algorithm for individualized treatment of endometriosis-associated pain based on a stepwise pharmacological approach for women not seeking conception and preferring medical therapy rather than surgery (modified from Vercellini et al., 2017).

contraceptive methods, patients should repeat pregnancy tests if they experience amenorrhoea. Finally, if prolonged periods of treatment are planned, they should undergo a dual-energy x-ray absorptiometry scan before starting treatment and periodically thereafter, unless they are willing to use add-back oestrogen–progestogen combinations and calcium plus vitamin D supplementation (Surrey *et al.*, 2018). All of the above may greatly influence treatment adherence.

In addition, Orilissa™ is much more expensive than CHC and progestogens. When faced with unaffordable treatments, some patients may choose to forego care (Vercellini *et al.*, 2016b, 2018c). It appears unclear why this drug would be a patient's preferred treatment, unless she did not respond to CHC and progestogens. Unfortunately, non-response to standard medications for endometriosis was an exclusion criterion in the trials published on elagolix.

The medical community's point of view: scientific information and the pharmaceutical industry's influence

Conflict of interest (COI) is a condition and not a behaviour. Nonetheless, it has been demonstrated that sponsorship of drug studies by the manufacturing company leads to more favourable results and conclusions than sponsorship from other sources (Flacco *et al.*, 2015; Lundh *et al.*, 2017).

The trials published on elagolix were funded by AbbVie and several industry employees were included among the authors (Carr *et al.*, 2014; Diamond *et al.*, 2014; Ng *et al.*, 2017; Taylor *et al.* 2017; Surrey *et al.*, 2018). External medical writers paid by the manufacturer are acknowledged in reports (Surrey *et al.*, 2018), and industry employees provided medical writing assistance (Taylor *et al.*, 2017). The majority of non-employed authors received money under different forms (Taylor *et al.*, 2017; Surrey *et al.*, 2018).

Indeed, an important issue in industry-sponsored reports is the way information is delivered and the perspective chosen when discussing data (Guo and Evers, 2013; Matheson, 2016; Liu *et al.*, 2017; Farquhar *et al.*, 2017, 2018), independently of 'the completeness and accuracy of the data and analyses and the fidelity of the trial to the protocol' (Taylor *et al.*, 2017).

Moreover, AbbVie is funding online continuing medical education on the diagnosis and treatment of women with chronic pelvic pain and endometriosis (e.g. https://www.medscape.org/viewarticle/892724, accessed on 7 August 2018; http://www.peerview.com/p/index.html?collection=150204858&presentation=150204858-p1&MemberID=101347395&EmailID=7565025&SpecialtyID=106&CountryID=110&ProfessionID=12&CampaignID=3414043&AOMID=28&Promocode=500#screen1, accessed on 28 August 2018) and, according to some authors, industry-sponsored education may foster over-diagnosis and over-treatment (Mintzes *et al.*, 2018).

Overall, the information on elagolix appears to be largely influenced by the drug manufacturer. Given the relevant implications for national healthcare systems and individual families, independent research on elagolix seems highly desirable.

Conclusion: elagolix for all or for some? the stepped-care approach

According to international guidelines, no major differences exist in the effect of available hormonal drugs used to relieve endometriosis-associated pain. However, differences exist in safety and tolerability profiles, as well as in cost of treatments (Dunselman *et al.*, 2014; Practice Committee of the American Society for Reproductive Medicine, 2014; National Institute for Health and Care Excellence, 2017). So how should elagolix be introduced into our therapeutic armamentarium (Perricos and Wenzl, 2017)? What is known is that elagolix relieves endometriosis pain in a dose-dependent manner. The same dose–response effect has been observed for untoward subjective and metabolic effects. This means that, if add-back therapies are not associated, substantial pain relief comes at the price of hypoestrogenic symptoms and BMD reduction. The long-term safety of elagolix will be defined by post-marketing studies. In practice, there do not seem to be sufficiently good reasons to consider elagolix differently from GnRH agonists and it should not be suggested as a first-line treatment for endometriosis owing to a suboptimal safety/efficacy/tolerability/cost profile. In other words, both GnRH agonists and antagonists should be used as rescue medications when low-dose CHC and progestogens are inefficacious, not tolerated or contraindicated in patients who prefer to avoid surgery.

Even if elagolix is proven superior to CHC and progestogens in terms of pain relief, this does not mean that it should be then prescribed to all patients with symptomatic endometriosis. Of relevance here, about two-thirds of unselected women with symptomatic endometriosis were successfully managed with continuous use of low-dose CHC, and only a small minority had to step-up to a costly progestogen or surgery (Vercellini *et al.*, 2018d). This stepwise approach (Fig. 1), developed together with a large national patient association (Vercellini *et al.*, 2018d), gave adequate pain relief and good overall patient satisfaction, at the same time minimizing the financial burden for women and their families and limiting opportunity costs.

A stepped-care approach is certainly not in the interest of the eight pharma industries that are currently developing GnRH antagonists for endometriosis (Guo and Groothuis, 2018) because resorting to these medications only in cases of failure of first-line treatments would imply a drastic reduction of revenues. However, the interests of patients and national healthcare systems do not always coincide with those of industry.

Authors' roles

P.V. conceived and drafted the original version of the article; P.Vi., G.B., L.B. and E.S. participated in the conception of the article; the members of the 'Luigi Mangiagalli' Endometriosis Research Group searched the literature, retrieved articles, extracted data, critically revised the intellectual content of the paper and approved the final version to be published.

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Conflict of interest

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Appendix

The 'Luigi Mangiagalli' Endometriosis Study Group

(Members are listed in alphabetical order).

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