Contraceptives with novel benefits

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Introduction: Progesterone receptor (PR) agonists (progestins) and antagonists are developed for female contraceptives. However, non-contraceptive applications of newer progestins and PR modulators are being given more attention.

Areas covered: The newer PR agonists including drospirenone, nomegestrol, trimedestone, dienogest and nestorone are being evaluated as contraceptives with health benefits because of their unique pharmacological properties. The selective PR modulators (SPRM; PR antagonists with PR agonistic properties) are under development not only for emergency contraception but also for other health benefits such as the treatment of endometritis and leiomyoma. After searching the literature from PubMed, clinicaltrials.gov and patent database, this review focuses on the effects and mechanisms of these progestins, and SPRMs as contraceptives with other health benefits.

Expert opinion: PR agonists and antagonists that have novel properties may generate better contraceptive effects with other health benefits.

Keywords: contraceptive, non-contraceptive benefits, progesterone receptor antagonist, progestin, selective progesterone receptor modulator

1. Introduction

Progesterone (P4) is a steroid hormone that is synthesized in the ovaries, the adrenal glands, the testes and the placenta. The classic action of P4 is exerted via binding to the progesterone receptor (PR), which belongs to the nuclear receptor superfamily that includes the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). When PR is bound by P4, the PR--P4 complex binds to the specific P4 responsive element of a target gene, regulating the expression of the gene.

To regulate the transcription of a target gene, the PR--P4 complex either binds with coactivators, which in turn favors the upregulation of gene transcription, or it binds with corepressors, which favors downregulation. A single human PR gene, residing on chromosome 11q13 [1], encodes two main forms, PR-A and PR-B, via different promoters [2]. The PR-A and PR-B are identical except for an additional 165 amino acids in PR-B [3]. This extra region in PR-B encodes a unique transactivation unit that leads to distinctive coactivator or corepressor recruitment from PR-A [3], creating cell-specific transactivation [4,5]. These distinct actions of PRs are proven by the selective deletion of either isoform. The ablation of PR-A in mice causes infertility and severe dysfunction of the ovary and uterus [6,7]. The deletion of PR-B causes malformation of the mammary gland, but the mice were fertile [6,7].

The classic action of P4 in the female reproductive system is to act on the PR, therefore, controlling ovulation, inhibiting the endometrial proliferation, and, in later stages of pregnancy, maintaining pregnancy [6,7].

P4 also becomes a neurosteroid after binding to a membrane P4 receptor or converting to another major neurosteroid, allopregnanolone. Allopregnanolone...
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**Article highlights.**

- Progesterone receptor agonists (progestins) and antagonists are developed for female contraceptives.
- Many new progestins have properties that contribute to non-contraceptive health benefits.
- Drospirenone is currently only available with EE as a combined oral contraceptive to treat acne and premenstrual dysphoric disorder.
- Nestorone is being developed as a long-term contraceptive such as in implant form and vaginal ring form.
- Newer selective progestin receptor modulators can be used not only as emergency pills but also as drugs for the treatment of uterine fibroids and endometriosis.

This box summarizes key points contained in the article.

acts as an agonist on the γ-aminobutyric acid (GABA) receptor in the neuron. As a neurosteroid, P4 affects synaptic functioning and exerts neuroprotective action [8].

The understanding of the role of P4 in female reproduction led to the development of synthetic PR ligands with either PR agonist (progestin) or PR antagonist properties. A progestin is a chemical that binds to the PR and triggers a response, mimicking the action of P4. As a contraceptive, a progestin can be used in combination with estrogen (e.g., in combined oral contraceptives, COC) or alone (progestin-only contraceptives). A progestin may bind to other nuclear receptors including AR, ER, GR and/or MR. These additional pharmacological properties of progestins may contribute to their non-contraceptive benefits.

A PR antagonist blocks the action of P4. A selective PR modulator (SPRM), such as ulipristal, varies its action in different tissues (agonist in some while antagonist in others) [9]. This mixed action raises the possibility of dissociation of therapeutic effects from unwanted effects of SPRMs. SPRMs have not reached the market yet neither as contraceptives nor as emergency contraceptives (ECs). They have non-contraceptive benefits including the treatment of leiomyomas and endometriosis. The major pharmacological roles of PR agonists and SPRMs are listed in Table 1. After searching the literature from PubMed, clinicaltrials.gov and patent database, in this review, we will discuss these PR agonists and SPRMs as contraceptives with novel benefits.

### 1.1 PR agonists (progestins)

The progestins include a range of steroids derived from different parent structures, which have those from P4 (17-hydroxyprogesterone derivatives and 19-norprogesterone derivatives) and androstene (drospirenone, DRSP, DS) as well as those from testosterone (19-nortestosterone derivatives; Table 2) [10,11]. Among the 17-hydroxyprogesterone derivatives are medroxyprogesterone acetate (MPA) and cyproterone. 19-Norpregesterone derivatives include nomegestrol acetate (NOMAC), nesterone (NES), trimegestone (TMG) and promegestone. Progestins that are derived from testosterone include estranes (norethisterone), gonanes (levonorgestrel (LNG), norgestrel, desogestrel (DNG), gestodene and norgestimate) and estranes/pregnanes (dienogest). The newer progestins, including DRSP, NOMAC, NES, DNG, TMG and promegestone, have been developed to eliminate the most unwanted androgenic effects.

The binding affinities of progestins to various steroid nuclear receptors have been evaluated in comparison with respective endogenous steroid hormones (P4 for PR, testosterone for AR, cortisol for GR, aldosterone for MR and estradiol for ER), and are summarized in Table 3. The newer progestins have their respective unique properties and are being developed as contraceptives, and also have other health benefits.

### 1.2 Drospirenone

#### 1.2.1 Pharmacological actions

DRSP is derived from 17α-spirolactone and has pharmacological actions similar to P4. It is devoid of estrogenic, androgenic and glucocorticoid activity, but has antimineralocorticoid activity [11-16]. Its antimineralocorticoid activity is one of its health benefits against the effect of estrogen on liver angiotension synthesis, which leads to water and salt retention [13,16]. DRSP has antiandrogenic activity [17], which can help in the treatment of acne.

#### 1.2.2 Pharmacokinetics

In women, DRSP is rapidly absorbed following oral administration. Its level peaks after 1.5 – 2 h, and the terminal half-life (t1/2) is about 32 h [12,17-19]. Serum DRSP levels were linearly correlated with oral doses of 0.1 – 10 mg DRSP [20]. DRSP is mostly bound to serum proteins, but not to sex hormone-binding globulin (SHBG) or corticosteroid-binding globulin (CBG) [18]. DRSP is metabolized in the liver [20,21].

#### 1.2.3 Contraceptive application

DRSP is used with ethinylestradiol (EE) in COCs; 3 mg DRSP/30 µg EE in 21-day/7-day (Yasmin) and 24/4 regimen (Yaz) have also been developed. The efficacy of 3 mg DRSP/20 µg EE is similar to older COCs, but with a more acceptable bleeding pattern [22]. In addition, a flex regimen of DRSP/EE is also in development.

#### 1.2.4 Non-contraceptive benefits

DRSP is being investigated as a possible treatment for acne. Two placebo-controlled trials were performed for 3 mg DRSP/20 µg EE to treat acne, and data showed that the COC was more effective than the placebo in treating moderate acne [23,24]. In other trials, 3 mg DRSP/20 µg EE was compared with two COCs (2 mg cyproterone acetate/35 µg EE [25] and 0.18 – 0.25 mg norgestimate/35 µg EE [26]), and results showed that 3 mg DRSP/30 µg EE was comparable with these acne-effective COCs. DRSP (3 mg DRSP/20 µg EE) has also been investigated to treat premenstrual dysphoric...
disorder (PMDD), and was shown to be very effective [27,28]. In addition, DRS in combination with E2 is also used for hormone replacement therapy (HRT; see review [29]).

1.3 Nomegestrol acetate

1.3.1 Pharmacological properties

NOMAC is a 19-norprogesterone progestin and does not exert any androgenic, estrogenic or glucocorticoid activities [30,31]. NOMAC has a potent antigonadotropic action, thus inhibiting ovulation at an oral dosage of 1.25 mg [32]. NOMAC shows moderate antiandrogenic activity although it is 20 times lower than that of cyproterone acetate, a potent antiandrogen [32].

1.3.2 Pharmacokinetics

NOMAC is rapidly absorbed and reaches a peak level within 2 – 3 h. The elimination t1/2 is approximately 50 h after oral administration to women [33]. NOMAC is highly bound to albumin, with negligible binding to SHBG and CBG. NOMAC is metabolized in the liver [33].

1.3.3 Contraceptive application

NOMAC is used with estradiol (E2) in COCs. An investigational COC containing 2.5 mg NOMAC/1.5 mg E2 in a 24/4 regimen is being developed. NOMAC/E2 had a robust ovulation inhibition [34]. A Phase III trial reported that NOMAC/E2 had less overall impact on hemostatic, lipid and carbohydrate metabolism than 150 µg LNG/EE 30 µg [35]. Clinical trials with a single silastic capsule containing NOMAC have shown high efficacy in preventing pregnancy [36,37]. This drug is approved by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in March 2011.

1.3.4 Non-contraceptive benefits

NOMAC has partial antiandrogenic activity, and is being tested for the treatment of menstrual disturbances, dysmenorrhea and PMDD [38,39].

1.4 Nestorone

1.4.1 Pharmacological properties

NES is a 19-norprogesterone derivative with a high PR affinity [40]. NES has very low AR binding affinity, and does not bind to ER [40]. At the dose required for contraceptive efficacy, NES binds to GR but does not exert glucocorticoid activity in vivo [40].

1.4.2 Pharmacokinetics

Administered parenterally, NES is highly potent, but orally inactive in humans [41,42]. Following a metered spray delivery of NES to women, serum NES peaks at around 20 h [43]. The elimination t1/2 of NES is 26.8 h [43]. In circulation, NES does not bind to SHBG [44,45]. NES is metabolized in liver to 4,5-dihydro-17α-deacetyl-nestorone [46].

1.4.3 Contraceptive application

Vaginal rings delivering 150 µg NES/15 µg EE have been evaluated as an investigational drug [47,48], and data show that it is effective for contraceptive purpose. A 2-year study of a single implant releasing 100 µg NES/day shows that there were no pregnancies in 2195 women circles and the users had less irregular bleeding compared with copper-T intrauterine device (IUD) subjects [49]. Another study with 150 women with 0.3 – 1.2 mg NES gel for 3 months showed that NES caused 53 – 83% suppressions on ovulation [48,49].

Table 1. Comparison of pharmacological actions of progesterone receptor agonist, antagonists and SPRMs.

<table>
<thead>
<tr>
<th>Pharmacological actions</th>
<th>Progesterone receptor agonists</th>
<th>Antagonists</th>
<th>SPRMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td></td>
<td>Inhibited</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibited</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable</td>
<td>Reduced</td>
</tr>
<tr>
<td>Pregnant uterus</td>
<td></td>
<td>Inhibited</td>
<td>Stimulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irregular</td>
<td>Amenorrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrophy</td>
<td>Amenorrhea</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>Fragile</td>
<td>Robust</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulation</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

Table 2. Classification of progesterone receptor P4 agonists/antagonists.

<table>
<thead>
<tr>
<th>Progesterone receptor agonists</th>
<th>Related to progesterone</th>
<th>Related to testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-Hydroxyprogesterone derivatives</td>
<td>Estranes</td>
<td>Norethisterone acetate</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Ethynodiol diacetate</td>
<td></td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Estrane/Pregnane</td>
<td></td>
</tr>
<tr>
<td>Androstene</td>
<td>Dienogest</td>
<td></td>
</tr>
<tr>
<td>Drosiphenone</td>
<td>Gonanes</td>
<td></td>
</tr>
<tr>
<td>19-Norpregesterone derivatives</td>
<td>Levonorgestrel</td>
<td>Norgestrel</td>
</tr>
<tr>
<td>Nomegestrol acetate</td>
<td>Desogestrel</td>
<td></td>
</tr>
<tr>
<td>Nestorone</td>
<td>Gestodene</td>
<td></td>
</tr>
<tr>
<td>Trimegestone</td>
<td>Norgestimate</td>
<td></td>
</tr>
<tr>
<td>Promegestone</td>
<td>Reduced</td>
<td></td>
</tr>
</tbody>
</table>

Selective progesterone receptor modulators

| Milepristone | Ulipristal acetate | Asoprisnil |

Cited from [10,11].

Adapted from [81].

SPRMs: Selective PR modulators.
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Table 3. Nuclear receptor binding of progestins.

<table>
<thead>
<tr>
<th>Relative binding affinity (folds)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>AR</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>3</td>
</tr>
<tr>
<td>Norethisterone acetate</td>
<td>1.3</td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>3.5</td>
</tr>
<tr>
<td>Gestodene</td>
<td>8.6</td>
</tr>
<tr>
<td>Third generation</td>
<td></td>
</tr>
<tr>
<td>Trimegestone</td>
<td>8</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>0.2</td>
</tr>
<tr>
<td>Norethisterone acetate</td>
<td>5</td>
</tr>
</tbody>
</table>

The data are adapted from respective references above.

AR: Androgen receptor; ER: Estrogen receptor; GR: Glucocorticoid receptor; MR: Mineralocorticoid receptor; PR: Progesterone receptor.

1.4.4 Non-contraceptive benefits

NES is being investigated as a potential HRT [50]. The parenteral administration of NES should be associated with fewer side effects. The nonprotective action of NES has been tested in rats and results have turned to be positive [51,52]. NES is demonstrated to promote myelination [53], thus a recent patent application has been claimed to treat multiple sclerosis using NES [54].

1.5 Desogestrel

1.5.1 Pharmacological properties

DNG is an orally active progestin. DNG has moderate affinity for PR in human [55,56]. It has no agonistic or antagonistic action on GR, MR and ER [56]. DNG inhibits ovulation at the minimal oral dose of 1 mg/day [55] without acting on central action on gonadotrophin secretion [57].

1.5.2 Pharmacokinetics

Serum DNG reaches peak level within 2 h, and the elimination t1/2 is around 10 h in women [10,58]. DNG does not bind to SHBG, but 90% bound to albumin [59,60]. DNG is metabolized in the liver [69].

1.5.3 Contraceptive application

DNG is developed in combination with EE in a COC (2 mg DNG and 30 µg EE), which shows that it has high efficacy and a well-tolerated rate [61]. It is also being tested for extended-cycle use with similar tolerated rate to normal cycle use [29]. DNG is used with E2 valerate (EV) in a COC. A COC containing 3 mg DNG/1 – 3 mg of EV was tested in a Phase III trial and data showed high efficacy [62], and had similar or less pronounced effects on hemostatic parameters than LNG/EE [63].

1.5.4 Non-contraceptive benefits

DNG has antiandrogenic activity [56], and can be used to treat acne [57]. DNG is also tested for the potential to treat endometriosis [64] and trials show that DNG/EV has high efficacy to treat heavy menstrual bleeding [65,66]. Long-term use of DNG shows a favorable efficacy to treat pelvic pain [67].

1.6 Trimegestone

1.6.1 Pharmacological properties

TMG is a 19-norprogesterone derivative [68,69]. TMG binds to human PR with an affinity greater than MPA [68]. TMG binds to the AR, GR and MR with low affinity, and has no measurable affinity for the ER [68]. It also has a weak antiandrogenic and modest antimineralocorticoid activity [68,69].

1.6.2 Pharmacokinetics

After single oral dose of TMG to women, TMG is rapidly absorbed with peak plasma level at 30 min [69]. The elimination t1/2 is 17 h. The pharmacokinetics of TMG is dose-dependent. TMG is highly bound to serum proteins. TMG is metabolized in the liver to its main metabolite TMG sulfate.

1.6.3 Contraceptive application

TMG is a potent progestin, with a good anti-ovulatory and anti-oestrogenic activity in the uterus [68]. The contraceptive potential of TMG delivered by a transdermal system has been explored, but so far no clinical trial has been published [70].

1.6.4 Non-contraceptive benefits

A double-blind trial over a 2-year period to compare the bleeding profile and endometrial safety in the postmenopausal women of 0.125 mg TMG/1 mg E2 with norethindrone acetate (NETA)/E2 was performed, and data showed that 0.125 mg TMG/1 mg E2 exhibited a more favorable bleeding profile than 0.5 mg NETA/1 mg E2 [71,72]. A trial was performed to compare 0.25 or 0.5 mg TMG/2 mg E2 with 0.5 mg NETA/2 mg E2 for the blood lipid profiles in postmenopausal women, and data also showed that TMG/E2 combination had a preferable profile to NETA/E2 combination [73]. A clinical trial using 0.125 mg TMG/1 mg E2 in the prevention of postmenopausal osteoporosis also demonstrated its effectiveness to treat this condition [74].

2. Selective P4 receptor modulators

Many SPRMs are derivatives of steroid compounds with mild or potent anti-PR activity. SPRMs may exert a contraceptive activity by different mechanisms such as inhibition of ovulation and disruption of endometrial synchronization. The synthetic SPRMs include ulipristal and asoprisnil. The potential clinical indications of SPRMs include EC, long-term estrogen-free contraception administered alone or in combination with a progestin-only pill to improve bleeding patterns [75].

2.1 Ulipristal acetate

2.1.1 Pharmacological properties

Ulipristal is a derivative of 19-norpregesterone. Unlike mifepristone, ulipristal appears to be a relatively weak GR
antagonist. It has no relevant affinity to ER, AR and MR [9]. Ulipristal is known to inhibit ovulation [9].

2.1.2 Pharmacokinetics
Ulipristal acetate is rapidly absorbed when orally administered to women, and its serum level peaks at about 1 h. The elimination t1/2 is approximately 32 h. Ulipristal acetate is metabolized in the liver.

2.1.3 Contraceptive application
In a preclinical study using rhesus macaques, an intravaginal ulipristal delivery can effectively induce endometrial atrophy and amenorrhea, providing the proof of principle as a contraceptive [76]. In a trial, women were given a single dose of ulipristal (10 – 100 mg) after ovulation and within 2 days of the LH surge it was found that ulipristal has contraceptive properties [77]. Ulipristal acetate is an effective EC for up to 120 h after unprotected intercourse [78].

2.1.4 Non-contraceptive benefits
Effectiveness of ulipristal in the treatment of leiomyomas has been performed in Phase IIb trial, and the trial proved that it was effective for controlling bleeding and reducing leiomyoma [79].

2.2 Asoprisnil
2.2.1 Pharmacological properties
Asoprisnil has an inhibitory effect on the ovary endometrium, and breast tissue, but has a partial agonistic effect on the myometrium of pregnant uterus. However, it inhibits the myometrial proliferation of leiomyoma. Asoprisnil does not affect estrogen secretion from the ovary, so its beneficial effects of estrogen on the bone and cardiovascular system are maintained. Asoprisnil had weak partial androgen agonist/antagonist effects in the Hershberger test in rats [80].

2.2.2 Pharmacokinetics
After administered orally at 5 – 25 mg/day, asoprisnil is well-absorbed [81]. The elimination t1/2 is 4 – 5 h [81]. It is metabolized in the liver, and the metabolite is found to have weaker agonist and stronger antagonist effects than asoprisnil [81].

2.2.3 Contraceptive application
Asoprisnil is possible for use as a contraceptive. However, it has not been tested for EC or long-term contraceptive.

2.2.4 Non-contraceptive benefits
Asoprisnil is being investigated to treat uterine fibroids in a Phase II trial [82]. In this study, asoprisnil (5, 10 and 25 mg) was administered orally once daily for 12 weeks, and data showed that asoprisnil suppressed both the duration and intensity of uterine bleeding [82]. A Phase III trial to treat uterine fibroids using asoprisnil with 10 and 25 mg was discontinued due to endometrial changes in patients [83], and it is unknown whether this drug will be marketed for treatment of uterine fibroids.

Asoprisnil is also being investigated to treat the pain from endometriosis. In a double-blind study, asoprisnil (5, 10 and 25 mg) was administered orally once daily for 12 weeks, and data demonstrated that all three doses significantly reduced pelvic pain/dysmenorrhea scores compared with placebo [84].

3. Conclusion
Many new PR modulators are under investigation for potential contraceptives with extra health benefits. Newer progestins have unique pharmacological and pharmacokinetic properties and are being developed as contraceptives with other benefits. DRSP is currently only available with EE as a COC to treat acne and PMDD. NES is developed for long-term use in a vaginal ring, implant and transdermal delivery forms. Ulipristal acetate, a SPRM, is not only being developed as a contraceptive, but also as a drug to treat uterine fibroid. Asoprisnil, another SPRM, is also under development for the treatment of heavy endometritis and leiomyoma.

4. Expert opinion
Many newer progestins and SPRMs are being developed for contraceptive use with non-contraceptive health benefits. The newer progestins display very low androgenic and glucocorticoid-like effects. Therefore, they have lower adverse effects. The combination of newer progestins with natural E2 instead of EE has potential for a major advantage.

Progestins with novel pharmacological and pharmacokinetic properties may have non-contraceptive health benefits. DRSP is currently only available with EE as COCs. These preparations have been indicated for the treatment of moderate acne due to its antiandrogenic activity. The unique advantage of DRSP as the progestin in such preparations lies in its antimineralocorticoid activity.

Several progestins such as DRSP and DNG have been indicated for the treatment of acne. The progestins can be used in combination with topical medications such as retinoids and antibacterial agents. Such combination therapy should lead to a more rapid effect and a greater improvement of the treatments.

The unique pharmacokinetics of NES renders its advantage for long-term delivery of the drug such as in a vaginal ring, implant and transdermal delivery system. The parenteral administration of NES should be associated with fewer side effects; however, the long-term safety of the drug warrants further evaluation. The neuroprotective action of many newer generations of progestin including NES could have novel benefits for degenerative neuron diseases.

With the great potential of new SPRMs for reproductive healthcare, it is possible to have new EC in near future. Ulipristal acetate has its functional and safety profiles similar to LNG and EC, while it has a longer window of action by suppressing a LH peak even when administered shortly before ovulation, a time when LNG is no longer effective. This

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Medical opinion expressed by Su, Lian & Ge

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Advantage appears to support ulipristal acetate as being superior to LNG for EC. As no surrogate parameter is available only the Pearl Index might be helpful in Phase III.

Newer SPRMs also have potential for the treatment of uterine fibroids and endometriosis. For example, asoprisnil, the first SPRM is being developed and reaches an advanced stage of trial for non-contraceptive health benefits, including the treatment of uterine fibroids and endometriosis.

The advances in molecular biology related to different coactivator and corepressor recruitment after the treatment of SRMs have the potential to explain the biological effects of SPRMs and to guide future drug discovery in this area.

In conclusion, PR agonists and antagonists that have novel properties may generate better contraceptive effects with other health benefits.

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Declaration of interest

The authors declare that they have no competing interests.

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