EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 8
435-452
Year: 2021

AN EXPLORATION OF ADHERENCE PATTERNS IN CONTRACEPTIVE PILL USERS FROM TECHNICAL AND EDUCATIONAL INTERVENTIONS: A META-ANALYSIS

Simran Sandhu, Patrick Ball and *Hana Morrissey

The University of Wolverhampton, United Kingdom.

***Corresponding Author: Hana Morrissey**
The University of Wolverhampton, United Kingdom.

Article Received on 12/06/2021 **Article Revised on 2/07/2021** **Article Accepted on 22/07/2021**

ABSTRACT

Background: Poor adherence to contraception has long been one cause of unintended pregnancies, emergency contraception and terminations. Oral contraception accounts for a largest group of contraception users and whilst there is a common understanding of general poor adherence, little is known about the impact of adherence interventions in this population. **Aim:** To explore the effectiveness of technical and non-technical interventions currently used or studied to encourage adherence to the oral contraceptive. **Methods:** Databases were used to conduct a comprehensive search of current literature including: PubMed©, ScienceDirect©, ClinicalTrials.gov and Cochrane© Library. CASP© criteria was used for the quality assessment of individual studies. RevMan® software was then used to analyse the data for a quantitative assessment and the qualitative data was analysed thematically. Adherence was assessed from the primary or secondary outcomes including number of missed pills, and continuation of oral contraception. **Results:** Seven studies including 4,226 women met the selected PICO© framework and had risk of bias moderate to low. Results from the meta-analysis demonstrated an overall increase in adherence with real time interventions OR=2.16, [1.65, 2.83] and continuation with knowledge interventions or text messages OR=1.50, [1.25,1.80]. A real effect was indicated with technical and educational interventions and outcomes but, the strength of the effect is weak. Individually however, a mean difference of only 0.5 missed pills resulted from one study (4.0 vs 3.5) (P=0.56) and in another, more participants actually missed pills in the text group (39% vs 27%) (p=0.4). Text messages also displayed positive differences in 6 month pill knowledge vs control (25.5 vs 23.7) (p<0.001) but digital tablet dispenser +/- acoustic alarm set promoted adherence. A greater percentage of participants missed zero pills, 70% vs control 24% (p=0.0001). Furthermore, an educational study revealed that 86% of women adhered to OC with tailored educational leaflets (OR 2.74, 1.21-6.21) yet another suggested summary leaflets were effective for understanding of all pill rules when questioned OR=4.41 (2.17-8.97). **Conclusions:** Adherence to the contraceptive pill remains less than optimal. Although educational and phone text messages interventions indicated only modest improvements in in some contraceptive pill users, it should not be completely disregarded. The long term benefits and cost-effectiveness of reminder tablet dispensers require more attention toovercome unintentional non-adherence.

KEYWORDS: Adherence, Compliance, Concordance, Community Pharmacy, Contraception.

INTRODUCTION

In 2018, in the UK there were more than 800,000 pregnancies in women of all ages with rates of conceptions increasing amongst women aged over 40 or under 18 (Corps, 2020). However, 45% of these pregnancies, or 1 in 3 births, were reported as unplanned (Public Health England, 2018). Pregnancy prevention or delay in women can be achieved by hormonal contraception which consist of a well formulated balance of the hormones oestrogen and progesterone to inhibit ovulation and sperm penetration. Whilst a variety of contraception methods exists, the most prescribed in the UK is the oral contraceptive pill (Davis and McIntyre, 2019).

Statistics revealed that 29% of the 51% female population utilise the pill as their main choice of contraception (Stewart, 2021). The choice of contraception is decided through an informed decision between the woman and her healthcare practitioner who will assess the patient onan individual basis and provide information accordingly. While this list is extensive, several factors are examined such as co-morbidities e.g. cardiovascular disease or migraines, the risk of STI's, current medication and the age of the patient. Alongside this, lifestyle and patient preferences form part of the consultation in addition to any legal and ethical issues if under 16 years of age (NICE CKS, 2019).

Other contraception methods are implants, injections, intrauterine contraceptive device or coil (IUD or IUS), patches, female tubal ligation and male vasectomy. Simple barrier methods like a diaphragm may only be effective for short-term use, others may have an intermediate effect (contraceptive patch). Surgical procedures are generally permanent (NHS, 2017b). The consultation is usually centred around the woman's requirements, future plans with family planning in addition to their attitudes towards contraception. Different methods of contraception will have varying degree of hormones in them, however they all work in similar ways depending on the type of hormone they contain (Joint Formulary Committee, 2020).

The hormone progesterone works by increasing the thickness of the cervical mucous, and reducing the amount thereby preventing the penetration of the sperm. These conditions are not favourable to the sperm. On the other hand, combination preparations that include progesterone and oestrogens have a dual mechanism by also supressing the release offollicular stimulating hormone (FSH) hormone and the phasic rise of lutienising hormone (LH) hormone which together, prevent ovulation (Waller and Sampson, 2017). Though hormonal contraception can be highly effective in birth control, it is not limited to pregnancy prevention. It can also be useful as treatment for conditions such as polycystic ovarian disease, hirsutism and menstrual disorders such as menorrhagia and dysmenorrhea (Health Guides, 2020). It has also commonly been used as a means of period delay for travel purposes (NHS, 2018). Adherence is the actions taken by the patients after agreeing to therapy plan to ensure that their medications are taken as prescribed. Non-adherence can be categorised as intentional (conscious) and non-intentional (unconscious) where intentional non-adherence refers to the conscious non-abiding behaviours (NICE, 2009). In contrast, unintentional non-adherence refers to patients willing to abide by treatments but are prevented to doing so as a result of barriers such as forgetfulness or inability to afford medication costs (NICE, 2009). Dwajani et al. (2019) determined five factors affecting adherence; patient related, treatment based, condition based, socioeconomic and health care system factors. Treatment cost is an example of a socioeconomic influence on medication adherence, however, this is not an issue in the UK as contraceptives are available for all ages, except for emergency contraception. However, transportation to a point of access for healthcare providers might be an unaffordable cost for many specially young females. Patient health literacy level enable them to access healthcare services (WHO, 2021). Conditions which require lifelong treatments may show a decline in adherence over time but persistent symptoms may act against such decline.

Currently, interventions to improve adherence are minimal and generic not aimed at specific users or conditions. Kini and Ho (2018) summarised six interventions used to improve adherence; reminders including simplifying medication regimens, patient education, frequent consultations, cognitive behaviour therapy (CBT) consultations and incentives. Although some reminder systems have been studied, they have not been widely implemented in practice due to cost. Mobile phone apps such as myPill® are readily available in the UK. The purpose of this app is to send out notifications to prompt users to take their pill but are not suitable for all types of phones and not promoted sufficiently by healthcare professionals (Stacey, 2020). These modern systems have not been sufficiently studied to determine their effectiveness.

Emergency contraception (EHC) is available as an oral pill supplied through community pharmacies with a pharmacist consultation (RPS, 2019; MHRA, 2021). In current practice, oral contraception pill (OCP) users are followed up by a doctor every 6 months and then annually providing there are no immediate concerns. During these visits, the doctors conduct physical checks and blood pressure measurement. It is expected that every 6-12 months the doctor or pharmacists assess the patient knowledge on missed doses, interactions with new medications and adverse effects, however, the current consultations time of 10 minutes is insufficient to perform all of those checks comprehensively but rather depends on the patient self-reporting (NICE CKS, 2021).

When contraception is taken for the purpose of pregnancy prevention a high level of adherence is required to prevent treatment failure. Despite the extensive use of contraception and the wide range of benefits, many individuals experience side effects such as nausea, headaches and altered moods and thromboembolic events which may lead to non-adherence (NHS, 2017a). Contraceptive blisters are marked with the days of the week, arrows in the calendar pack aim to guide and remind pill users the days of the week and the week of the cycle. Most women find the calendar packs sufficient to guide their use, but only if they do not have other emotional disorders or cognitive impairment that cause loss of motivation to self- care or forgetfulness.

Review Rational and Aim

An overview of current practices highlighted the lack of continued care available to users of the contraceptive pill, to support their adherence and continuation of the pill. It is uncertain whether reduced adherence seen arises from a lack of interventions e.g. compliance aids for this population, or simply due to human nature and behaviour (Waller and Sampson, 2017). This review aimed to explore and evaluate the interventions available to improve women's adherence to the oral contraceptive pill.

Methods and Search Strategy

This systematic review meta-analysis used the PRISMA-

P© (Appendix 1) protocol and quality check of studies methods and designs used in each study were examined in relation to specific criteria using CASP© checklist (Appendix 2). Randomised Controlled Trials (RCTs) were selected for this review. The selection criteria was developed using the PICO© framework (Table 1).

Table 1: PICO framework.

Patient or Populations	**Inclusion:** Female patients aged 13 years or over Non-pregnant females taking OCP or starting OC with a desire to not currently become pregnant Females who have access to technology e.g., a smartphone **Exclusion:** Females using other than OCP methodsPregnant patients Male patients
Interventions	Non-technical interventions Educational leaflets or educational pocket cards Technology-based interventions such as text-messages, phone call follow ups Reminder cards and digital tablet dispensers with or without reminder alarms
Comparators	Medical Standard Care Pharmacy Counselling
Outcomes	Primary Outcomes • Increased or reduced adherence • Time delay of pill released from the pills containerSecondary Outcomes • The rates of subsequent follow ups • The number of females who missed taking the pill • The number of missed pills • Continuation of OCP • Change in knowledge on the OCP • Pregnancy (clinical outcome)
Search words	"adherence" OR "compliance" OR "concordance"; "medication adherence aids" OR "adherence technology"; "contraceptive pill" OR "oral contraception" OR "contraception failure"; "randomised controlled trial".

Search Results

Seven studies matched the PICO framework and identified as randomised controlled trials so were suitable for inclusion (Figure 1 and Appendix 3). Seventeen studies were excluded from the analysis. This was due to differing study designs, outcome measures and contraceptive methods. Four studies were excluded as a result of their study design. Two studies were prospective cohort studies (Jay et al 1984; Lachowsky & Levy Toledano, 2002). Two studies were pilot studies (Gilliam, Knight and McCarthy 2004; Sahlman, Matero and Kärkkäinen 2018). A number of studies focus on different contraception methods rather than oral contraception alone. Three trials focused on the Depo-Provera® injection method (Canto De Cetina, Canto and Luna 2001; Keder, Rulin and Gruss 1998; Trent, Thompson and Tomaszewski 2015). One study assessed adherence to the contraceptive ring (Gilliam et al., 2010). Another evaluated the effects of interventions when using emergency contraception (Schwarz, Gerbert and Gonzales, 2008). Eight trials concentrated on interventions to aid contraception choice (Ferreira et al 2011; Garbers et al 2012; Hughey et al 2010; Langston, Rosario and Westhoff 2010; Schwandt et al 2013; Smith et al 2018; Torres et al 2014; Zhu et al 2009).

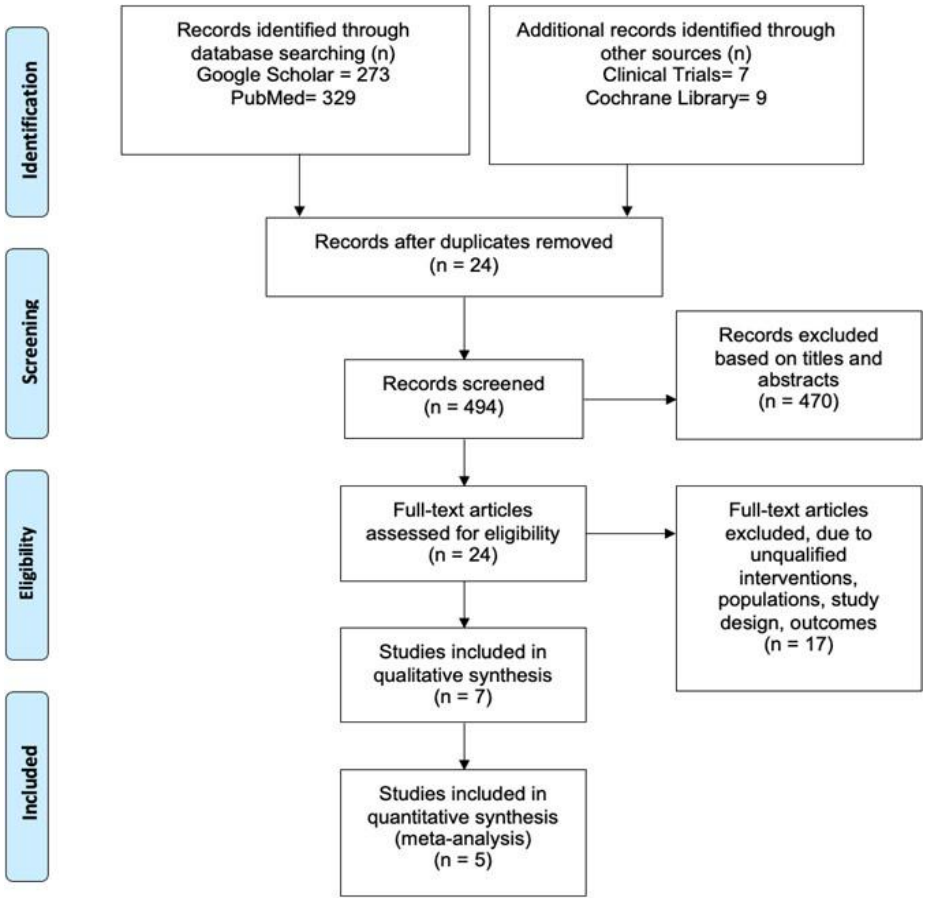

Figure 1: Search Strategy Flow Diagram.

Study CharacteristicsSetting

Four studies were conducted in a single location or family planning centres in the USA (Berenson and Rahman 2012; Castaño et al 2012; Hall, Westhoff and Castaño 2013; Hou etal 2010). Garbers et al. (2012) was also directed in the USA but here, two family planning centres were included. Only one trial identified as a multi-centre study consisting of 42 locations across 4 countries which included France, Italy, Spain, Germany and the UK (Wiegratz et al., 2015). One of the earliest and most comprehensive studies was limited to the UK only and included 15 general practices' (Little et al., 1998).

Sample size

Approximately half of the studies collated had a sample size ranging between 630 to 1155 participants. Similar sample sizes were acknowledged between two separate studies (659 and 636). The total number of participants from all studies is calculated as 4,226. Power calculations for sample sizes were conducted within some studies (Castaño et al 2012; Houet al 2010; Little et al 1998; Wiegratz et al 2015).

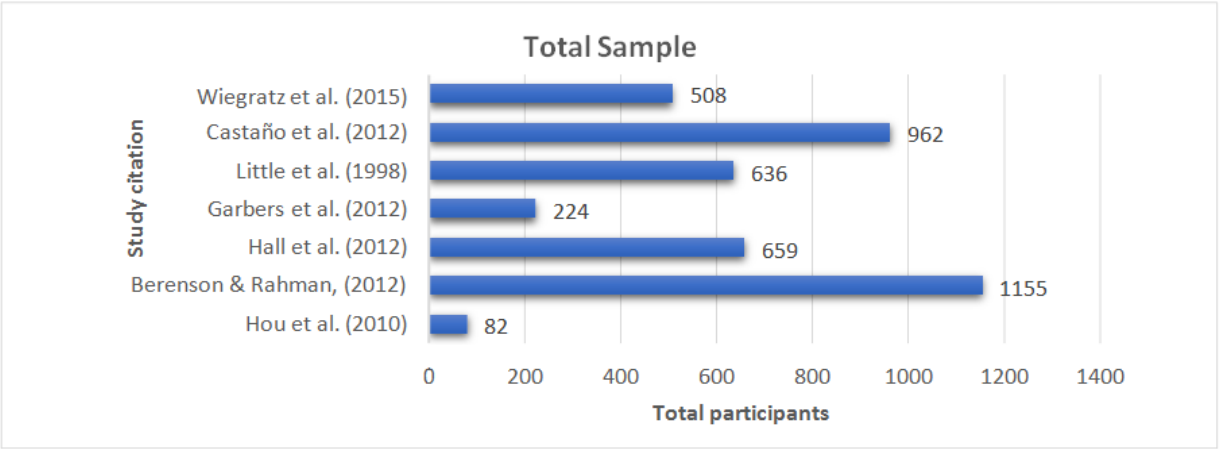

Figure 2: Summary of study populations.

Population
One trial recruited women aged between 18-35 years (Wiegratz et al., 2015). The highest age limit was in the trial by Little et al. (1998) where women aged up to 45 years were included (18-45 years). Only 3 trials included females aged 18 years and under, 16-24 years,16 years+ and 13-25 years (Berenson & Rahman 2012; Garbers et al 2012; Hall, Westhoff and Castaño 2013). Out of these 3 trials, only one study recruited the youngest females aged 13 years (Hall, Westhoff and Castaño, 2013). Castaño et al. (2012) did not specify any age ranges but did state women younger than 25 years of age were suitable for inclusion criteria. Hou et al. (2012) did not identify any ages for inclusion in their methods. Baseline participant characteristics were similar across all studies but only one study excluded women with current or past use of OC that lasted longer than 1 month (Berenson and Rahman, 2012).

Interventions
Educational or counselling: Three studies focused on educational interventions to influence adherence (Berenson and Rahman 2012; Garbers et al 2012; Little et al. 1998;).

Technology: Three trials used text messages to address adherence (Castaño et al 2012; Hall, Westhoff and Castaño 2013; Hou et al 2010). One trial implemented a digital tablet dispenser with or without acoustic alarms (Wiegratz et al., 2015).

Outcomes
Three trials measured the continuation of contraception (Berenson & Rahman 2012; Castaño et al 2012; Garbers et al 2012). Two trials measured the number of missed pills. However, two of these trials simultaneously assessed continuation of OC and the number of missed pills (Berenson & Rahman 2012; Castaño et al 2012). On the other hand, two studies measured knowledge of contraception and rules using knowledge scores (Hall, Westhoff and Castaño 2013; Little et al 1998).

Follow up (Time to outcomes)
Average follow up of participants across all studies was between 3-6 months. Three trials followed up participants 6 months from baseline (Castaño et al 2012; Hall, Westhoff and Castaño 2013; Little et al 1998). Combination of follow up periods of 3, 6 and 12 months was seen with another study (Berenson & Rahman, 2012). Contrarily, a four month period was adapted by one trial (Garbers et al., 2012). Wiegratz et al. (2015) had more frequent and multiple follow ups from week 3, 11, 23, 35 to 51 weeks post initiation.

RESULTS
The majority of the studies included most of the relevant information for a quantitative assessment. Trials where data was missing were still included for discussion because of the lack of studies available on adherence to OC's using different interventions.

Although outcomes were similar across the studies found, the limited number of studies found and grouped into each outcome, was too little to generate accurate effects. A total of four studies were excluded from this statistical analysis. Hall, Westhoff and Castaño, (2013) and Berenson and Rahman, (2012) were omitted from the quantitative assessment due to insufficient individual data. Two others were excluded as other comparative studies were restricted (Hou et al 2010; Little et al 1998). These studies explored significant interventions and outcomes, so will be discussed further in the qualitative assessment.

Assessment of outcomes from statistical data by Castaño et al. (2012) and Wiegratz et al. (2015) revealed some similarities in methods and so, these studies were suitable for inclusion in a forest plot. The second comparison consisted of Garbers et al. 2012 and Castaño et al. (2012) as they assessed the same outcome (continuation of OC).

Outcome 1
In this comparison, the studies were grouped according to the statistical methods used. Wiegratz et al. (2015) had a smaller sample size, but enabled larger effects alone (OR=3.69). Castaño et al. (2012) had a larger sample size but individually, resulted in a lower effect OR=1.72 [1.25,2.38] yet still favoured the new interventions over control. Independently, acoustic tablet dispensers OR=3.69 [2.20, 6.18] displayed greater effectiveness compared to text messages OR=1.72 [1.25,2.38]. Combined together, both studies favoured the new interventions to enable an overall effect of OR=2.16, [1.65, 2.83], with no overlap of the CI from both studies. The results suggest that there is a stronger effect from the combination of technical interventions on reducing the number of pills missed thus increasing the number of women missing zero pills in a given period. The intervention in Wiegratz et al. (2015) was significantly successful alone, but the wider confidence intervals imply the results were less reliable. More attention on reminder tablet dispensers is therefore required by researchers to fully understand the effects of tablet dispensers and missed pills.

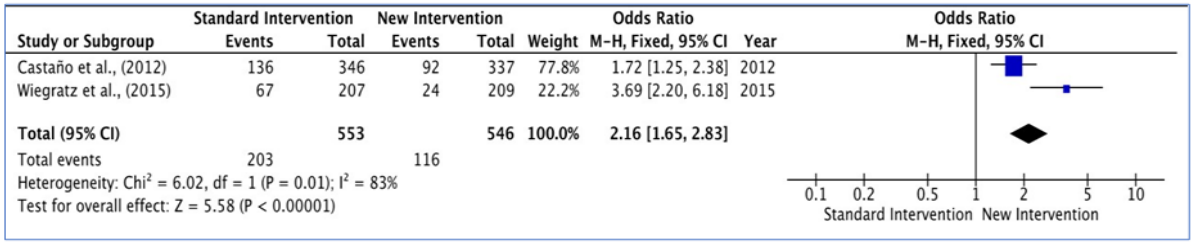

Figure 3: Forest plot. Comparison 1, Adherence to OC from the number of participants missing their pill.

The forest plot revealed statistical significance of p<0.00001 but a large heterogeneity of I^2 =83%. The higher overall heterogeneity may be attributed to the differences in methodology between the two studies. Study weighting between both trials differed highly (77.8% vs 22.2%) and although they both measured the same outcome (adherence to OC) and tested technical interventions opposed to educational interventions, the interventions still differed. Wiegratz et al. (2015) used tablet dispenser with or without acoustics whereas Castaño et al. (2012) used text-messages. In terms of settings, Wiegratz et al. (2015) conducted a multicentre study in four countries including the UK but the Castaño et al. (2012) trial was refined to one location only, New York. As a result of these differences, the heterogeneity is raised.

Outcome 2

In comparison 2, the effect size was also measured as odds ratio. Here, the individual and overall pooled effect favoured the study interventions in comparison to the control. There was no obvious overlap of the 95% CI lines between the two studies. Despite the overall effect favouring the new interventions marginally OR=1.50, [1.25,1.80], the total heterogeneity was still significantly high (I^2 =73%). Greater differences between the weighting of these two studies 1.4% vs 34.4% as well as the subgroup analysis, will have somewhat contributed to the sizeable heterogeneity (Castaño et al 2012;Garbers et al 2012). The clinical significance overall here was also p=0.00001 indicating a true effect with the interventions and continuation of the pill so rejecting the null hypothesis. This extreme value however, may be aresult of the population size (Dahiru, 2008).

For the study by Castaño et al. (2012), a subgroup analysis was performed based on the day of follow up. The subgroup analysis calculated a lower percentage of heterogeneity of 52.4% however, as this value is still high, it can be a consequence of the timescale of follow up and subsequent results. More individuals (483) were followed up at ≥ 188 days yet only 200 participants were followed up at ≤ 187 days therefore accurate 6 month continuation results were not fully achieved. Overall, follow up at ≤ 187 days resulted in a lower % of participants who were OCP users however, follow up at ≥ 188 days resulted in more users of OCP at that time. Surprisingly, interventions yielded similar results in the follow up periods; 60% vs 54% and 75% vs 54%. This was reflected in the forest plot when the 95% CI of ≥ 188 days positioned directly on the line of no effect. To a lesser extent, follow up at ≤ 187 days favoured the new intervention group as the CI did not touch the line of no effect meaning OR > 1. More defined follow up periods or very close follow up periods would benefit a true effectand heterogeneity.

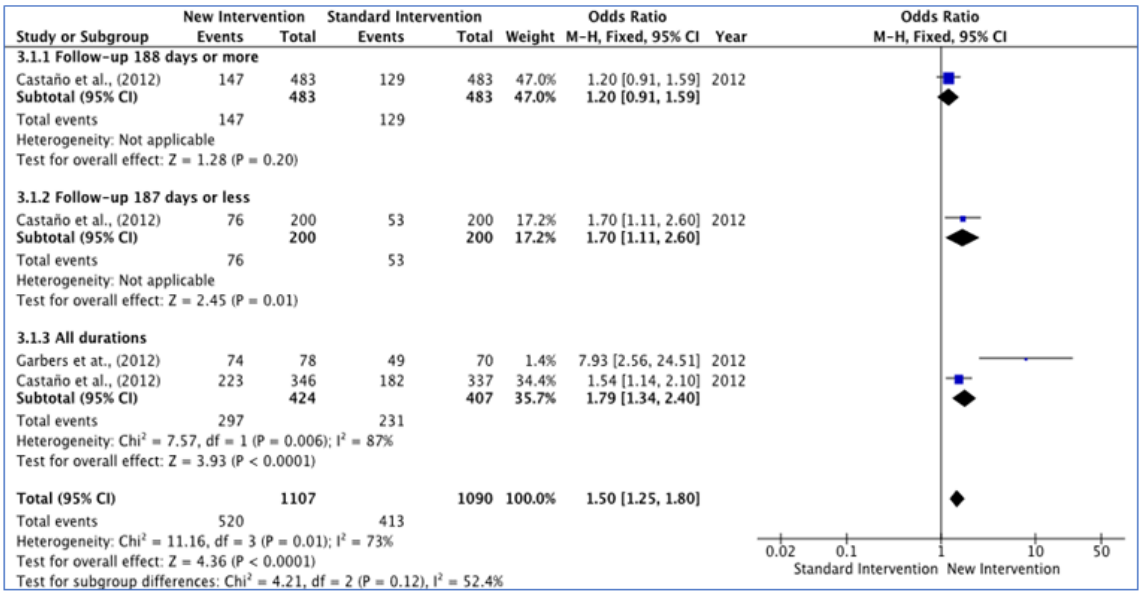

Figure 4: Forest plot. Comparison 2, continuation of OC by number of days with subgroup analysis.

Summary of quantitative assessment

In summary, both forest plots revealed OR > 1, adherence to the pill OR=2.16, [1.65, 2.83] and continuation of the pill OR=1.50, [1.25,1.80]. Whilst this indicates a real effect between the interventions and outcomes, the strength of the effect is still considerably weaker. The weakest correlation was between the exposure of interventions on continuation outcome. Daily text messages do not heavily impact the desired outcome of adherence neither continuation of the pill, yet acoustic tablet dispensers alone can produce desirable results of adherence. On the other hand, educational leaflets in combination with text messages may lead to greater continuation. Although the comparisons included similar interventions and outcomes, the higher level of heterogeneity implies greater differences in study characteristics such as location of study, design, patient populations and potentially the interventions and outcomes.

Risk of Bias

Assessment of the risk of bias in individual studies and across studies was completed using a risk of bias tool (Deeks et al., 2021). (See Appendix A-G).

Allocation: All of the 7 studies reported on randomisation but only 5 studies specified a method for sequence generation. Two trials used a random number table (Castaño et al 2012: Hall et al 2012). Three trials used computer assisted sequences (Garbers et al 2012; Hou et al 2012; Wiegratz et al 2015). Sequence generation was unclear from two trials despite randomisation (Berenson & Rahman 2012; Little et al 1998).

Blinding: Many of the studies were open label, where participants were aware of interventions to which they were assigned, but the study investigators were not. This is likely to be attributed from the intervention types, making it difficult to blind participants so neither single blinding or double blinding was achieved. Four trials were investigator blinded (Berenson & Rahman 2012; Garbers et al 2012; Hall et al 2012; Hou et al 2012). Blinding was not reported in 3 studies therefore, it was assumed that both participants and investigators were not blinded (Castaño et al 2012; Little et al 1998; Wiegratz et al 2015).

Selective reporting: Garbers et al. (2012) also reported adherence in addition to continuation as an outcome but did not specify the individual data or how it was assessed. **Other bias:** Little et al. (1998) sent out questionnaires on contraception knowledge to participants opposed to testing knowledge within their general medical practices. One study allowed women to turn off the acoustic alarm in the tablet dispenser intervention group (Wiegratz et al., 2015). Other studies relied on self- reporting. Berenson and Rahman (2012) relied on medical records and telephone interviews to measure effects of outcomes. Hou et al. (2010) concomitantly allowed women to report via diaries and the electronic monitoring device.

Overall bias

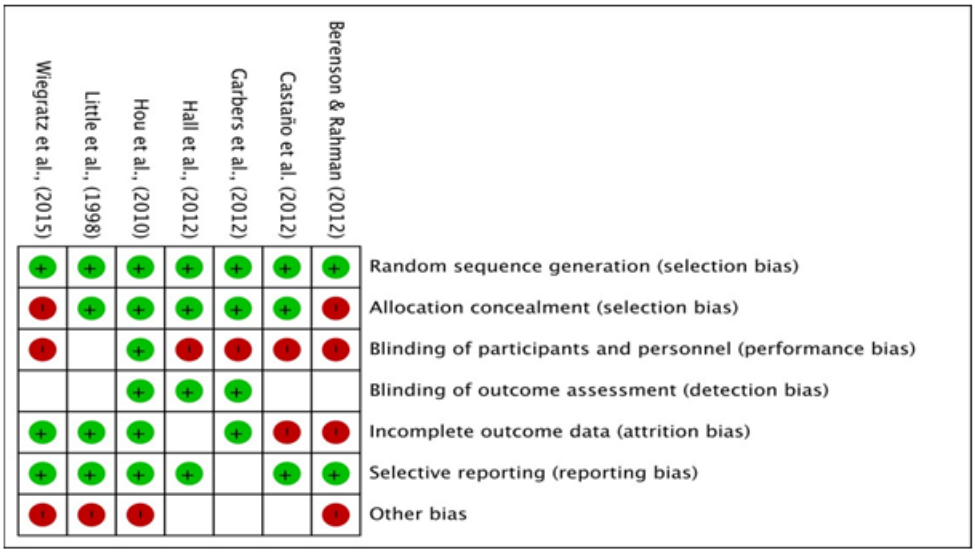

Figure 5: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

DISCUSSION

Educational Interventions

Three studies (Garbers et al 2012; Little et al. 1998; Berenson and Rahman 2012) focused on educational interventions to influence adherence. Focusing their research on patient knowledge made the results more applicable to intentionally non-adherent women, women who knowingly and intentionally do not take their contraceptive pills.

Berenson and Rahman (2012) used educational interventions in two study arms; face to face behavioural counselling and monthly follow up telephone calls for up to 6 months in addition to face to face counselling. This study found that no intervention had a substantial effect on improving adherence. Although the number of women who missed pills were notably higher in the control group, each study arm showed overall decreases in missed pills. In the control group, 103 (32.7%) women reported missing a pill in the past 3 months compared to 89 (28.7%) in the clinic-based intervention group and 94 (30.0%) in the clinic and telephone group (p=0.54). Despite fewer missed pills in the interventions arms at 3 months, data was still very similar across each study arm at the 6 and 12 month follow ups: Both displayed a decrease in missed pills by almost 50% across all study arms, the control, the clinic and the clinic plus telephone groups; 50 (18.7%), 43 (15.9%), 50 (18.2) respectively at 6 months and 25 (11.7%), 24 (11.2%) and 17 (7.8%) at 12 months. As the results of the interventions are similar across each study arm, the benefits of these interventions are still questionable. These results may be affected by the demographics including age of participants who were, on average, 20 years old. Barrier methods (condoms) were used by partners highly in the first 3 months in all study arms, but use decreased over time. Even though the encouragement of barrier methods are important, this may have increased the number of participants missing pills if dual methods were in use. Furthermore, patients who are prescribed medication may not commence their course straightaway, therefore post intervention follow ups may not be accurate or representative when real-time data is not available and may possible be applied to this study in terms of unknown bias.

In comparison, Garbers et al. (2012) used contraceptive learning modules and educational leaflets to impact knowledge of contraception. Out of the study population (n=190), the greatest adherence was acknowledged with tailored interventions (86%) compared to generic and control (65% and 69%). Women who received tailored handouts showed a strong correlation of adherence with this intervention type; 86% of women adhered to contraception OR 2.74 (1.21-6.21). Generic interventions showed no marked differences or improvement in knowledge compared to the control group. Only 65% displayed adherence OR=0.81 (0.40- 1.64) implying a weak association between this intervention and the outcome of adherence. As adherence in this study was not determined by the number of missed pills, the results on adherence are not clear. Despite stating that adherence was measured on the basis of last use within 2 weeks, the study did not reveal how many missed days accounted for poor or moderate adherence. However, using the intention to treat approach, pre-existing bias was reduced as women started contraception on the day of initial visit rather than before baseline. Moreover, at 4 month follow ups, 85% (n=190) of women continued to use the contraception but continuation was highest in the tailored intervention group (95%) compared to control (77%) (p=0.002). Continuation was measured by asking women whether they are using their contraception at follow up. As continuation was assessed alongside adherence, it gives healthcare professionals a chance to discuss if women discontinued, the reasons why and to suggest alternative methods.

Little et al. (1998) assessed the knowledge of three specific categories of pill rules; pill failure, subsequent action and emergency pill during consultation and at 3 months. It was established that single and uncomplex interventions such as summary leaflets demonstrated usefulness in increasing knowledge, compared to multiple or complex interventions such as family planning leaflets. This was more prominent when asking questions with the summary leaflet; more women were aware of the 3 important rules. With no questions, 28% of women were knowledgeable on the rules but this later increased with questions, 39% of women had a better familiarity when asked questions. Even the control group (no leaflet) showed an increase with questions from 12% to 26%. However, as questions were sent to the home it poses a great limitation to this result because it is unknown whether any other sources were used or if the knowledge specifically arose from the leaflets given at baseline. It was also suggested that 3 months is an ideal length of time to show long term improvements in knowledge but Woolliscroft (2020) emphasised the 'Ebbinghaus' forgetting curve' in general populations, where an average of 90% is forgotten in 28 days when presented with new information. This suggests frequent engaging discussions with the patient is a better approach than using self-report questionnaires at the 3rd month. Another limitation was that the study stated educational leaflets allowed women to improve their knowledge on 'pill rules' but did not assess the current or future adherence from this gained knowledge.

In summary, the educational interventions may achieve only modest improvements in adherence but this type intervention should not be abandoned completely. Although knowledge on the contraceptive pill may not fully reduce the number of missed pills, it will educate most women on the subsequent actions to take. As leaflets are widely used to date, summary leaflets covering the most important rules or information require more attention.

Technological Interventions

Aside from the more conventional interventions as such leaflets, the most common themes around technical interventions were text-messages used by three RCTs (Hall, Westhoff & Castaño 2013; Hou et al 2010; Castaño et al 2012). Hou et al. (2010) adapted their method simultaneously utilizing an electronic device attached to the pills which served as a monitoring device tracking the date and time of pill release. A similar study used a pill dispenser, however in this study, pill removal, was prompted by an alarm on the dispenser and a text-

message on the dispenser device itself rather than a mobile phone (Wiegratz et al, 2015).

Hall, Westhoff & Castaño (2013) implemented daily text messages for 6 months which ranged from educational messages, to a personalised message aiming to assess knowledge rather than number of missed pills. The study measured differences in means as the primary measure. It was agreed that educational text messages improved knowledge, as the mean scores at six months were (25.5) but only (2.7) ($p<0.001$) in those without text messages (control). OC knowledge was broken down into 6 domains; MOA, effectiveness, use, benefits, side effects and risks.

Only slight improvement was shown on "risk" knowledge scores from 3.3 to 3.4, and no there was no difference between text message intervention and control (3.4 vs 3.4) ($p=0.87$). Scores on "benefits" displayed greatest improvement as a percentage change in points was 13 (text intervention) vs 9 (control) ($p<0.001$). Although knowledge was assessed at baseline and at 6 months, assessment on future knowledge would be beneficial as there is a higher chance of forgetting learnt knowledge in the long term. As outcomes were assessed in terms of knowledge rather than number of missed pills, the results only give an insight into adherence. Improvement in knowledge of "benefits" of OC may encourage the most adherence but as scores on risk did not differ between the groups, it may further compromise adherence. Several drawbacks were realised in this study. One example was when women received almost repetitive daily text messages for 180 days, this may exacerbate poor adherence as the recipient may become accustomed to ignoring the messages if they are not captivating.

According to Hou et al. (2010), generally, adherence was lost with increasing time. The number of missed pills increased with a growing number of weeks as well as the cycle number and suggested that overall, adherence was not improved. In general, the mean number of missed pills were 4.0 ± 3.5 pills by women in the text message group and 3.5 ± 3.4in the control group ($P=0.56$) with an approximate mean difference of 0.5 missed pills. Nelson et al. (2017) revealed that high adherence is best described as missing only 1 or less pills a month but here, there was an average of four missed pills therefore portraying poorer adherence in both groups despite using text messages. Additionally, the non-significant differences in the number of missed pills between the use of intervention (text-message) andno intervention (control) may be the result of characteristics that were not controlled. Previous use of OC, reminders with OC and use of EHC can influence the patterns of adherence shown by the women and because of these criteria, adding to the risk of bias. The study also showed that women did not report accurately in their diaries. The electronic device revealed that 4.9 ±3.0 pills were missed in the text message group but only 1.4±1.9 were recorded in diaries. Similar patterns were seen in the control group, 4.6 ± 3.5 (electronic monitoring) and 1.1 ± 1.2 (diaries) which indicates the need of appropriate adherence measures in practice. On the other hand, the electronic monitoring device helped reduce bias in the trial as it collected real time data on the number of missed pills alongside self-reporting.

Similarly, Castaño et al. (2012) revealed that a text message intervention did not completely eliminate the missing of the contraceptive pill. The number of missed pills did significantly reduce and on average only 1 missed pill was stated. In reality, the possibility of this may be uncertain as Hou et al. (2010) reported that an average of 4 pills were missed with text messages. It was also reported that 39% of women missed zero pills compared to control 27% ($p=0.04$) during the last month from follow up. This unexpected data can be a result of the difference in time to follow up for each woman as well as women self-reported the outcomes during interview. Once again, this adds to bias as it is unknown whether the women actually remembered the exact number of pills during the course of approximately 180 days. Continuation of use outcome showed that 64% vs 54% ($p=0.005$) of women were still OCP users at the time of follow up. This 10% difference implies that there is a stronger effect on continuation with text messages compared to no text message alerts. The continuers were also categorised into discontinuers and continuers according to their baseline characteristics. This gave an insight of likely behaviours of certain populations. Mean differences between continuers and discontinuers showed that of continuers, more were employed (61% vs 47%), older in age (21.3 ± 2.4 vs 19.9 ± 2.6) and had previous use of oral contraception (83% vs 68%). As continuers were most likely to still miss an average of 1 pill, text message intervention require optimisation. Acoustic tablet dispensers may overcome this limitation.

Wiegratz et al. (2015) collected real time data from the assessment of acoustic and non- acoustic tablet dispensers. The primary outcome of mean time of pill release delay between both study arms were 88 minutes vs 180 minutes respectively with a mean difference of 90 minutes. Even though delay of the pill was longer in the control group (deactivated acoustics), the time delay of 88 minutes is still a great deal. It is assumed that the acoustic prompt would encourage women to take the pill straightaway. Regardless, the acoustic pill dispenser builds routine and ensures that the window of delay is decreased thus, preventing the likelihood of double dosing. While assessing the number of participants that missed pills (secondary outcome), this trial also explored several other significant factors and secondary outcomes that were not identified or explored in other RCTs. Contraceptive efficacy, satisfaction of use and more importantly tolerability were the additional secondary outcomes assessed. This was the sole study that had a focus on tolerability with EE/drospirenone$_{flex}$ where

17.6% (n=88) of women experienced more than one ADR directly related to the contraceptive pill. Regular ADRs were nausea (2.2%), headache (3.2%) and breast pain (2.6%). Though these ADRs are not rare findings, they may help understand adherence patterns as stated in the study, 6.0% (n=30) of women as a result of these ADRs, discontinued the pill. Whether this was on their own initiative or by investigator recommendations is unknown. The study was labelledas a multicentre study yet only 535 women were randomised therefore giving minimal representation of each country demographics.

Whilst only RCTs were chosen for review, several non-randomised controlled trials and smaller scale studies have explored important interventions. A more recent but non randomised controlled trial conducted a pilot study which implemented an electronic device with an on-demand reminder attached to a pill strip. The reminder system reduced the number of missed pills from 1.9% to 0.3% and enabled some pill taking regularity by decreasing the time by 1 hour and 32 minutes ($p<0.01$) (Sahlman, Matero and Kärkkäinen, 2018). In contrast to the tablet dispenser used by Wiegratz et al. (2015), this device was connected to a smartphone device. One prospective cohort study also used a technical intervention, the reminder card was programmed to elicit audible bleeps as a reminder. With use, 74% women reported full compliance during the 3 months and 46% of these women were those who were most likely to simply forget. The study did not explore the reasons for forgetting to take the pill despite using the card, such as side effects or simply not carryingthe card with them (Lachowsky and Levy-Toledano, 2002).

In order to understand the patterns of adherence in contraceptive users and other conditions, a RCT investigating adherence to medication in type 2 diabetes was evaluated. This study used text message interventions and found that less pills were missed with this intervention (15%) opposed to the control (19%), ($p=0.065$). The medication monitoring system revealed that the pill release delay was lower in the text messaging group, 50% of patients released the tablet within an hour compared to 39% without text messages (Vervloet et al., 2012). Comparably, Wiegratz et al. (2015) found that reminder alarms allowed quicker pill release (126 minutes vs 140 minutes). Faster responses in diabetic patients compared to OC users can be a result of patient perception of urgency to treatment. Since most diabetic medicationsare taken after food, it may account for the reduced delay. Patients on anti-diabetic medication are on life-long medication, whereas contraceptive pill users may only take the pillfor shorter lengths of time making adherence harder in these pill users due to difficulty in maintaining a routine.

Overall, it can be concluded that text messages have little effect on number of missed pills in the short term but may encourage continuation and reduce missed pills in the longer term. Educational text messages show positive changes in knowledge but it's resultant effects on adherence is less certain. In contrast, significant adherence was achieved with acoustic tabletdispensers in short-medium term use but more attention is required to this intervention type as only one RCT explored acoustic tablet dispensers.

Measuring adherence

There is no gold standard for measuring adherence. Measures are classified as direct or indirect. A systematic review summarised both measures; direct measures focus on the concentrations of drug in the blood and indirect measure cover questionnaires, electronic databases, pill counts and electronic monitoring. This review found that two methods may enable better differentiation of adherent and non-adherent patients in a study population (Anghel, Farcas and Oprean, 2019). It is important to be mindful of methods that may overestimate adherence and provoke reporting bias from self-reporting or pill counts. Pill counts are easier and inexpensive but are not always reliable (Jimmy and Jose, 2011).

Measuring adherence was major consideration lacking with all of the included studies. Measuring adherence is difficult and subject to bias through patient reporting. Whilst focusing on adherence to the contraceptive pill, those interventions which consisted of devices (e.g. tablet dispensers or reminder cards), overlooked adherence to these devices itself (Lachowsky and Levy-Toledano 2002; Wiegratz et al 2015). This brings an added difficulty of remembering to carry the device or card.. The tablet dispenser interventions showed a lower number of missed pills which may be a result of women with genuine forgetfulness, yet it is uncertain whether the pills were actively ingested by other users who are intentionally non- adherent. Video observed therapy (VOT) may overcome this limitation. In an RCT assessing adherence in tuberculosis patients, VOT was found to aid in dosing regimens and increase continuation of treatment. Real-time VOT allows live assessment of patients ingesting their medication through video call whereas in non-real time VOT, patients can pre-record themselves and upload. Then, healthcare professionals can then assess their adherence (NHS, no date).

However, text messages intervention and VOT measure of adherence both pose certain limitations. For instance, in the case of a OC user without a mobile phone or when on silent mode, the user may miss the pill altogether, simply won't be able to record themselves or access video calls. Generalised measures of adherence include telephone consultations. They are effective in terms of gathering qualitative data and gaining a better background understanding of the attitudes of users, but the ease of conducting them may not always be straightforward. As discovered by Berenson and Rahman (2012), often, several telephone calls are required to reach the patient. Post contraceptive initiation or intervention follow ups are timely and costly to the NHS

and when they are not feasible (unable to reach the patient), follow ups are lost contributing to the reduced adherence to OC.

Amongst the seven studies, only one study actively screened for 'direct' signs of non- adherence. Initially general signs such as body weight were screened for, through to more accurate measures such as urine analysis testing for unintended pregnancy (Wiegratz et al., 2015). This was beneficial as initial signs may not reveal pregnancy and weight gain may be contributed from lifestyle factors or the pill rather than pregnancy itself. These direct measures may be time consuming in practice and can often accurately measure non adherence when pregnancy is revealed. However, negative pregnancy results may not always represent adherence to the pill. There might be changes in their sexual activity and some may result to barrier methods instead.

Limitations

Populations: A number of the studies analysed studies the effects of interventions in younger females which is to the assumption that these adolescents have limited knowledge on contraception. This therefore overlooks the females or adults who are simply just forgetful (unintentional non-adherence) despite having sufficient knowledge as well as overseeing adults who may not have knowledge despite being a long term or frequent user of contraception.

A number of studies reported past use of OC and current use of OC at the time of study initiation which will impact data through bias. These women may or may not have an increased knowledge or understanding of OC use at baseline and may have potentially already built a routine to the pill taking patterns thus increasing adherence.

Most studies overlooked patients with co-morbidities. These women may have better adherence due to a build-up of routine however, if co-morbidities are vast, routine thus adherence may be lost as a result. Castaño et al. (2012) did report on co-morbidities and stated that 17% took other medications alongside the pill. Future trials should report co- morbidities and coexistent medications in baseline characteristics to draw links between adherence and the contraceptive pill. Only younger women were assessed in some studies so this lack of data may be justifiable.

Blinding

The trials included were all open label where the participants at least knew about the interventions assigned to. This was almost unavoidable due to the nature of the studies and as different interventions were studied rather than different medications. However, it may still somewhat affect data on adherence to interventions through reporting. Majority of the studies were still randomised so minimising cofounding risks and in most studies, investigators were blinded during randomisation of participants.

Outcomes

Four studies analysed continuation of OC as another outcome (Hall et al 2012; Castaño et al 2012; Garbers et al 2012; Berenson and Rahman 2012). Continuation of the contraceptive pill doesn't necessarily suggest adherence as one may continue to take the pill despite a number of missed days or doses. In spite of that, continuation alongside the least amount of missed pills, would present with higher adherence. A larger scale analysis of secondary outcomes was also lacking. Little to zero information was available on safety or tolerability alongside adherence which may be an influencing factor on adherence itself. One study explored the knowledge of some women on efficacy on one clinical outcome (pill failure), yet did not assess the actual outcome amongst users (Little et al., 1998). Wiegratz et al. (2015) investigated both efficacy and tolerability together with the number of missed pills. The design of some studies relied on self-reporting of outcome data through the use of patient diaries and during telephone interviews (Berenson and Rahman, 2012). In contrast, Little et al. (1998) assessed any gained knowledge of participants through home sentquestionnaires, possibly limiting the chances of true answers. Hall, Westhoff & Castaño (2013) gathered outcome data via a combination of methods, telephone interviews and knowledge questionnaires. The majority of the studies only assessed adherence up to a yearand follow up periods were often less than a year with a common period of 6 months. Future trials should look to assess the long term benefits of these interventions in frequent pill users. Many women will not be frequent users of OC for example as a result of altered sexual habits. If a routine is initially built up by the individual, this cycle would be interrupted as a result of this non-frequent usage. Likewise, follow ups should be conducted in timely intervals, around 3 months, as patient attitudes may change during their journey making follow-up of greater importance for timely adjustments. This would be more important when adherence is poor due to side effects, but early detection will improve adherence. This will only benefit a single type of user, and unintentional non-adherent users would still be overlooked. Nevertheless, it may encourage a change of regimen such as 21-day pack or 28-day pack.

Location

A number of study locations were examined in the USA and other countries. Even though patient characteristics may be similar in the UK, the healthcare systems differ widely. Women may have little access as a result of factors such as cost of treatment or consultations with healthcare providers. According to the American Pregnancy Association (2017), women in the US spend approximately $60-$360 (£44- £261) annually for just their monthly pill supply and $20- $200 (£14-£145) initially on consultations. Individual costs are dependent on their healthcare cost packages. This can ultimately

impact the adherence patterns and increase rates of unwanted secondary outcomes such as pregnancy and abortions. On the other hand, free of charge contraception is available to women in the UK and so, missed number of pills may be lower thus refill rates may be higher.

Comparisons to other reviews

The earlier review by Smith et al. (2015) researched the effects of mobile phone based interventions to improve contraception use or adherence in comparison to clinic based intervention or counselling. A more recent, comprehensive analysis by Mack et al. (2019) however, analysed the effects of multiple interventions compared to standard care. Outcomesfrom this review were similar to previous studies but here, there was an additional focus on adverse effects as a determinant of adherence.

This review differs from both of these reviews as it focuses on OC only rather than other methods or formulations. Tablet-based contraception is the most common type ofcontraception and due to the nature of its mechanism, it is taken every day for 21 or 28 days compared to for example, DMPA injection which requires less frequent administration. The aim therefore, was to reflect on patterns of adherence in pill users more closely to acquire a better understanding of these users.

CONCLUSION

This analysis concludes that adherence to the contraceptive pill remains poor. The meta- analysis agreed that there is only modest improvements of adherence with text-messages alone. Acoustic tablet dispensers however, reduced missed pills significantly and aided in pill taking regularity. As a result, these would most useful in those patients with unintentional non-adherence compared to those who intentionally reject treatment. On the other hand, educational interventions displayed improvements in knowledge but little is known about its relation to adherence. These studies often disregarded their definitions of adherence and assessed knowledge but not the resultant adherence from this gained knowledge. Therefore, educational interventions should aim to assess missed pills to reflect adherence outcome more closely. Only a few studies understood the complexity behind non-adherence and adapted interventions accordingly. Studies often overlooked adherence to their actual trialled devices or interventions so future trials should aim to minimise complex interventions.

Differences in results suggest there are different types of OC users but there is not a single intervention that can be applied for all of these users. Ultimately, adherence interventions are patient specific, women would need to be assessed individually and thoroughly before implementation of one or more interventions. Where patients are perceived as high risk of non-adherence, a combination of interventions can be applied; reminders, more frequent follow-ups (3-6 months) and pill reviews to maximise not only continuation but adherence and treatment outcomes. Specifically, this review suggests personalised messages to prompt engagement of OCP users alongside real-time tracking of adherence itself where available and if cost effective. More importantly, both adherence interventions and optimised methods to measure adherence should be employed.

AKNOWLDGEMENTS: N/A.

Conflict of interest: No conflicts of interest to declare.

Funding: No external funding.

Authors contributions: SS: Concept and design of study, acquisition of data, analysis and interpretation of data; PB: Supervised the concept and design of study development, analysis and interpretation of data, drafting the article and approval of the version to be published; HM: Critically review of the article and the version to be published

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Appendix 1: Review Protocol

Step 1: Initial Search

The initial searches were conducted using Google scholar, a single data base. This was to identify and gain an understanding of the quantity of studies, types of studies and the data currently existing in relation contraception. The existing data gave an overview on the expected 'outcome' which was decided as adherence.

Step 2: Database search

Here, a more refined search was adapted which was led by using some standard search techniques such as free-text searching, boolean logic and truncation. The second search was a more comprehensive search where further databases were included and consisted of: PubMed, ScienceDirect, ClinicalTrials.gov and Cochrane Library.

Step 3: Screening

The titles and abstracts of each study were initially screened which unmasked a number of methods used for adherence at present. The individual interventions in each study were then grouped into either 'interventions' and 'comparators' as part of the PICO.

Step 4: Verification

Studies that were deemed eligible during screening were further assessed on an individual basis owing to the PICO formed.

Step 5: Bibliography search

Eligible studies were further evaluated by checking each reference list. The reference lists were examined for potential studies to include. Steps 3 and 4 were then repeated.

Step 6: Documentation

The overall search was recorded to process each stage and to refer to if required at a later time. After the search was complete, a total of seven applicable studies were retrieved and were included in the analysis.

Step 7: Quality Assessment

The credibility of the studies found during the search were further examined using CASP criteria checklists (CASP, 2020).

Step 8: Risk of bias Assessment

The risk of bias was assessed in each study and was completed using a risk of bias tool (Deeks et al., 2021). Individual bias in each study was assessed according to 5 important factors:

- Randomisation process bias
- Bias from deviations from intended interventions
- Bias due to missing outcome data
- Measurement of outcome bias
- Selection bias

Overall bias from each study was rated under 3 categories:

- Low risk of bias- no concerns across all five factors
- Medium risk of bias- some concerns in one of the five factors
- High risk of bias- some concerns in several of the factors

Step 9: Data extraction and management

Data was extracted individually from the included studies and was presented in a summary of characteristics table. Where possible, data was then collated and inserted into RevMan© V5 for assessment. Data on excluded studies were presented descriptively.

Step 10: Missing Data

Where possible, missing data was calculated using the provided data. However, studies that had individual or raw data missing was excluded from the quantitative analysis but was analysed descriptively. This was due to the limited time-scale of this review so it was not possible to contact the researchers for more information where data was limited.

Step 11: Synthesis of results

RevMan© Manager Software was used to present the qualitative data (RevMan, 2020).

Step 12: Summary Measures

The meta-analysis assessed only dichotomous data. The number of events in intervention and control groups were analysed using the Mantel-Haenszel method and odds ratio with a 95% confidence interval.

Step 13: Assessment of Heterogeneity

A interpretation guide was used to assess the potential levels of heterogeneity from the studies collated(Deeks, Higgins and Altman, 2021).

- 0% to 40%- potentially not important
- 30% to 60%- moderate heterogeneity
- 50 to 90%- substantial heterogeneity
- 75% to 100%- considerable heterogeneity.

Appendix 2: Quality check

Berenson & Rahman (2012)	Risk of Bias	Author Judgement
Random sequence generation (selection bias)	Unclear	Randomisation scheme developed by the UTMB Office of Biostatistics using PLAN procedure followed for allocation but specific sequence not mentioned.
Allocation concealment (selection bias)	High	Not reported.
Blinding of participants and personnel (performance bias)	High	Single blinded, participants not blinded.
Blinding of outcome assessment (detection bias)	Unclear	Single blinded.
Incomplete outcome data (attrition bias)	High	Data on patients in each group reported.
Selective reporting (reporting bias)	Low	Information on outcomes available in results.
Other bias	Unclear	Some outcomes and intervention group relied on self-reporting data.

Garbers et al. (2012)	Risk of Bias	Author Judgement
Random sequence generation (selection bias)	Low	Computer assisted block randomisation using nondeterministic algorithm.
Allocation concealment (selection bias)	Low	Block randomisation using computer nondeterministic algorithm which is determined by deci second when participant entered the survey.
Blinding of participants and personnel (performance bias)	High	Single blinded.
Blinding of outcome assessment (detection bias)	Low	Single blinded.
Incomplete outcome data (attrition bias)	Low	Patient outcome data provided using logistic regression model.
Selective reporting (reporting bias)	Unclear	Information on pre-define outcomes available in results.
Other bias	Unclear	Used qualitative assessments (questions) to measure outcomes.

Wiegratz et al. (2015)	Risk of Bias	Author Judgement
Random sequence generation (selection bias)	Low	Randomised in 1:1 ratio from two groups using an interactive voice response system/interactive web recognition system.
Allocation concealment (selection bias)	Low	Randomised in 1:1 ratio from two groups using an interactive voice response system/interactive web recognition system.
Blinding of participants and personnel (performance bias)	High	Open label.
Blinding of outcome assessment (detection bias)	Unclear	Open label.
Incomplete outcome data (attrition bias)	Low	Data on patients in each group reported.
Selective reporting (reporting bias)	Low	Detailed information and data on primary and secondary outcomes available in results.
Other bias	Unclear	Participants in intervention group were allowed to turn of the acoustic alarm off.

Castaño et al. (2012)	Risk of Bias	Author Judgement
Random sequence generation (selection bias)	Low	1:1 fixed allocation with blocks of 4. Sequence generated by random-number table.
Allocation concealment (selection bias)	Low	Assignments placed into sequentially numbered, sealed opaque envelopes.
Blinding of participants and personnel (performance bias)	High	Open label.
Blinding of outcome assessment (detection bias)	Unclear	Open label.
Incomplete outcome data (attrition bias)	High	All patient data provided.
Selective reporting (reporting bias)	Low	Information on pre-defined outcomes available in results.
Other bias	Unclear	Baseline characteristics e.g. past OC use.

Hou et al. (2012)	Risk of Bias	Author Judgement
Random sequence generation (selection bias)	Low	Computer generated with varying blocks of 4 and 6.
Allocation concealment (selection bias)	Low	Sequences concealed within opaque, sequentially numbered envelopes until interventions assigned by a non-researcher.
Blinding of participants and personnel (performance bias)	Low	Investigator blinded.
Blinding of outcome assessment (detection bias)	Low	Investigator blinded.
Incomplete outcome data (attrition bias)	Low	Data on patients in each group reported.
Selective reporting (reporting bias)	Low	All pre-defined outcome data available.
Other bias	Unclear	Design/baseline characteristics e.g. past OC use, use of barrier methods.

Little et al. (1998)	Risk of Bias	Author Judgement
Random sequence generation (selection bias)	Low	Randomised into 1 of 6 groups in a 3 x 2 factorial design.
Allocation concealment (selection bias)	Low	Numbered opaque envelopes. Blank leaflet added for control to match weights of envelopes.
Blinding of participants and personnel (performance bias)	Unclear	Not reported or assumed open label/ unblinded.
Blinding of outcome assessment (detection bias)	Unclear	Not reported or assume open-label/unblinded.
Incomplete outcome data (attrition bias)	Low	All relevant patient data provided.
Selective reporting (reporting bias)	Low	Data on all outcomes assessed (knowledge)
Other bias	Unclear	Design e.g. assessment of outcomes through self-report questionnaires.

Hall et al. (2012)	Risk of Bias	Author Judgement
Random sequence generation (selection bias)	Low	Participants were randomly assigned in a 1:1 fixed allocation ratio to intervention: control.
Allocation concealment (selection bias)	Low	Random assignments generated by random number table and placed into sequentially numbered, sealed, opaque envelopes. Envelopes later opened at recruitment site.
Blinding of participants and personnel (performance bias)	High	Blinding of study staff but not participants.
Blinding of outcome assessment (detection bias)	Low	Blinding of study staff but not participants.
Incomplete outcome data (attrition bias)	Unclear	Overall data provided but not individual patient data.
Selective reporting (reporting bias)	Low	All pre-defined outcome data present.
Other bias	Unclear	Baseline characteristics e.g. past OC use.

Appendix 3: Summary of study characteristics

Study/ Author	Intervention (I)	Comparator (C)	Population	Intervention duration and follow up	Outcome	OR [95% CI] X^2 Mean, S.D.
Castaño et al. (2012)	Text message	Standard care	N= 962 Mean Age (I)= 20.8 ± 2.5 (C)= 20.4 ± 2.7 Race (I)= African American (39%) (C)= African American (45%) Setting=New York	6 months	Continuation of OCP at follow up Missed zero number of pills	(I)=75% (C)= 54% P=0.003 (I)=39% (C)=27% P=0.04
Garbers et al. (2012)	Tailored handouts with module Generic handouts with module	Standard care[a] with module	N= 224 Mean age= 29.1 Race= 73% Hispanic Setting= 2 locations across USA	4 months	OC continuation Adherence to chosen method	Tailored (I)= 2.74 (1.21- 6.21) P= 0.016 Generic (I)= 0.81 (0.40-1.64) P= 0.557 (C) P= 0.507
Hou et al. (2010)	Text-message reminder With electronic monitoring device	Standard care[a] With electronic monitoring device	N= 82 Mean age= 22 Race= 79% white Setting= 1 clinic in Texas (USA)	3 months	Missed number of pills	(I)= 4.9 ± 3.0 (C)= 4.6 ± 3.5 P = 0.60
Berenson & Rahman, (2012)	Clinic-based Clinic-based + telephone	Standard care	N=1155 Mean age= 19.9 Or 56% 16-19 years, 44% 20-24 years Race= 54% Hispanic Setting= 1 clinic in Texas (USA)	At 3 months, 6 months then 12 months	Missed number of pills OCP continuation	Clinic (I)= 0.80 (0.63-1.03) Clinic + telephone (I)= 1.09 (0.86-1.40) (C)= 1.00
Little et al. (1998)	Summary leaflet +/- questions Family Planning Association leaflet +/- questions Interactive questions	Standard care	N= 636 Mean age= 26.5 Setting= 15 general practices in England	6 months	Knowledge scores	No Questions: Summary (I)= 4.04 (1.68-9.75) Family Planning Association (I)= 3.43 (1.45-8.09) (C)=1.00 Questions: Summary (I)= 6.81 (2.85 to 16.27) Family Planning Association (I)= 2.58 (1.07-6.18) (C)= 3.03 (1.30-7.07)
Hall, Westhoff & Castaño, (2013)	Educational text messages	Standard care	N= 659 Mean age= 21 years Race= 41% African	6 months	Knowledge scores	(I)= 25.5 (C)= 23.7 P=0.001
Wiegratz et al. (2015)	Tablet dispenser with alarm	Tablet dispenser without alarm	N= 508 Mean age= 25.5. Race= 86.4% Caucasian Setting= 42 locations across France, Italy, Germany, Spain & UK	3, 11, 23, 35 and 51 weeks	Pill regularity/ daily pill release time Missed zero number of pills Efficacy and tolerability	(I)= 88 ± 126 (C)= 178 ± 140 P < 0.0001 (I)=70% (C)=24% P<0.0001
a= no intervention	±= mean and standard deviation					