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Same gain, less pain: potential patient preferences for adjuvant treatment in premenopausal women with early breast cancer

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Abstract

The aim of this study was to determine the treatment preferences (adjuvant goserelin or cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy) of healthy premenopausal women should they hypothetically develop oestrogen-receptor (ER) positive early breast cancer. Two hundred pre or peri-menopausal women read two scenarios describing goserelin or chemotherapy. Information included: How and where treatments were administered, side-effects, their likely persistence and impact on fertility. Women stated their unprompted initial and final preferences with reasons for the choices made. Respondents showed an overwhelming preference for goserelin. 156 (78%) women favoured goserelin, 22 (11%) chemotherapy and 22 (11%) remained undecided ($P < 0.0001$). Primary reasons for preferring goserelin for were 105 (71%) avoidance of chemotherapy side-effects, especially hair loss, perceived convenience and less disruption to normal life 54 (36%). The minority who preferred chemotherapy, valued the treatment finishing more quickly. These results together with clinical trial data showing equivalence of goserelin with CMF regimens suggest that premenopausal women with ER-positive tumours should at least be offered the choice of either adjuvant hormone therapy or chemotherapy.

Keywords: Goserelin; CMF; ER+; Pre-menopausal; Early breast cancer; Patient choice

1. Introduction

Oophorectomy in premenopausal women with hormone receptor-positive tumours produces significant reductions in the annual rates of tumour recurrence and death [1–3]. In randomised studies, both surgical oophorectomy and switching off ovarian hormone secretion using gonadotrophin-releasing hormone (GnRH) agonists appear as effective as chemotherapy with the cyclophosphamide, methotrexate and fluorouracil (CMF) regimen [2,4–8]. Studies comparing chemotherapy alone with a combination of GnRH agonists and tamoxifen have suggested that combination of these hormonal agents may be superior to CMF chemotherapy in improving breast cancer survival [9]. Further studies comparing these agents with anthracycline-containing chemotherapy regimens are underway. Despite published evidence showing that hormonal therapy, at least in trials to date, appears equivalent to chemotherapy in appropriately selected patients, few patients are offered the choice between these two treatment options. When there are treatments of equal efficacy, but where these treatment options have very different effects on quality of life, then there is a strong case for providing information about different treatments and offering patients choice. GnRH analogues, such as goserelin, and chemotherapy have different modes of administration

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and their side-effect profiles vary significantly, so these agents have different impacts upon quality of life.

Whereas chemotherapy requires regular hospital outpatient visits, goserelin can be administered monthly by a primary-care physician or a community nurse. However, chemotherapy is usually finished in 18–24 weeks, but goserelin treatment continues for two to three years. The side-effects of GnRH agonists are similar to those of women entering the menopause and include development of hot flushes, sweating (particularly at night), vaginal dryness, loss of libido and possibly also mood swings [10–12]. Once treatment finishes, theoretically, these symptoms should cease and most women then return to their previous premenopausal state and remain fertile. The major side-effects of chemotherapy include fatigue, nausea/vomiting and hair loss [13]. Chemotherapy can also induce premature menopause with the associated development of infertility, which in many cases is permanent. In one report, only 23% of goserelin patients were amenorrhoeic at three years compared with 77% of those treated with chemotherapy [14]. One study of quality of life found early benefits at three to six months for women receiving goserelin compared with those receiving chemotherapy, with patients receiving goserelin requiring significantly less effort to cope with their illness and its treatment. By three years, there had been a positive change in quality of life for both groups, with no significant difference between the groups [12]. In another study, whereas menopausal side-effects diminished at the cessation of endocrine therapy, patients treated with chemotherapy reported continued problems three years after starting treatment [11].

Both treatments have their advantages and disadvantages and the difference in side-effect profiles between these two agents may provide a "spectrum of choice" for patients and clinicians [15]. However, in reality doctors often struggle to integrate results from quality of life studies into clinical practice, yet provision of this information is vital to patients if they are going to make an informed choice about treatments [16,17]. Why patients choose a particular treatment is poorly understood and doctors often make assumptions based on age or the perceived intelligence of the patient [18]. Of interest, when patients are asked directly about their thoughts on cancer treatments, their answers are often not those predicted. For instance, patients considered symptoms considered by doctors as relatively minor such as a change in weight or sore mouth, to be just as influential in determining their choice of treatment, as late, more permanent morbidity [19]. In today's climate of patient participation in decision-making and ensuring informed consent, it is important that patients are given adequate information about different treatment options, including how these treatments impact upon their quality of life. Furthermore, it is important that doctors are open-minded about their patient's concerns and preferences with regard to the different treatments offered [16,20].

The study reported here assessed the preferences of a group of healthy premenopausal volunteers should they hypothetically develop oestrogen-receptor (ER) positive breast cancer. Reasons why women either chose or rejected treatments were explored together with any socio-demographic variables associated with their choices. The study was conducted in the South East of England and had Local Research Ethics Committee approval.

2. Patients and methods

2.1. Assessments

Study-specific assessments were designed. Scenarios describing either goserelin or chemotherapy treatment were constructed using published data and information from cancer charity websites. These were modified following feedback from five experienced breast cancer consultants and three specialist breast cancer nurses. The scenarios explained how each treatment was administered, the side-effects and their likely persistence after treatment completion, the impact on fertility, and any subsequent treatment such as tamoxifen that might be needed. Table 1 shows the side-effects as listed in the scenarios. Care was taken to emphasise that the number and severity of side-effects varies from person to person and that some treatments are available to ameliorate

Table 1
Side-effects of each treatment

Goserelin	Chemotherapy
Common side-effects	*Common side-effects*
• Hot flushes and/or night sweats	• Tiredness, sometimes extreme fatigue
• Periods will probably stop	• Nausea, sometimes vomiting
• Mood swings	• Hair loss (partial or complete)
• Weight gain	• Periods stopping/becoming less frequent
• Feeling of fuzzy headedness	• Hot flushes and/or night sweats
• Vaginal dryness	• Changes in bowel habit e.g. constipation
• Decreased sexual desire	• Mouth ulcers
	• Weight gain
	• Memory/concentration problems
	• Vaginal dryness
	• Decreased sexual desire
Less common side-effects	*Less common side-effects*
• Fluid retention	• Achy joints
• Bone pain or achy joints	• Depressed immune system leading to higher chance of getting an infection which may require hospitalisation
• Nausea	

side-effects, The chemotherapy scenario included a statement saying that the side-effects would usually ease off between cycles of treatment, whereas in the case of goserelin it was stated that the side-effects would be likely to last for the duration of treatment.

A short questionnaire was designed to gather information about each woman's age, menopausal status, partnership status, number and age of children, educational qualifications, whether anyone close to them had experienced cancer, the type of cancer and any treatment given. Post-codes were obtained to determine Carstairs deprivation scores [21]. The scenarios and demographic questionnaire were pilot tested for clarity and ease of completion on women of different ages and educational backgrounds and modified accordingly.

2.2. Sample and data collection

The target sample comprised 200 pre- or peri-menopausal women aged between 25 and 49 years and who had not had cancer. The number of women in each age group was stratified to reflect the incidence of breast cancer diagnosis per age group of the United Kingdom (UK) population [22], see Table 2.

Women were recruited using a variety of means including: E-mail messages sent to university staff, advertisements placed around campus, direct approaches to people in public places such as railway stations and large department stores, and snowballing techniques via colleagues and friends. Potential participants were seen face to face by a researcher who gave them a brief information sheet explaining the study and those who consented to take part read the scenarios and completed the questionnaire. Approximately 20 women who were approached directly declined participation most usually because they lacked the time, and a further 30 were deemed ineligible at the outset, predominantly because they were outside of the age range or were post-menopausal.

The presentation order of the treatment scenarios was counterbalanced, so that half the women read the goserelin scenario and half the chemotherapy scenario first. The following paragraph prefaced each scenario:

Table 2
Stratification of study sample by age group[a]

Age group (years)	*N* (%) newly- diagnosed cases 1998	*n* in study
25–29	202 (3)	5 (3)
30–34	675 (8)	17 (9)
35–39	1345 (17)	34 (17)
40–44	2262 (28)	57 (29)
45–49	3470 (44)	87 (44)
Total	7954 (100)	200 (100)

[a] Percentages are slightly different between cases and study subjects due to rounding.

Imagine you have recently been diagnosed with breast cancer and have already had surgery to remove the cancer. Next, you see a specialist who talks to you about two different follow-up treatments to prevent the cancer coming back. Research has shown that each treatment is equally effective, but they have different side effects. YOU must decide which treatment to have.

Each woman's treatment preference was then elicited using three response options – goserelin, chemotherapy or undecided. The primary reasons for their treatment choices were recorded, initially by means of free responses then prompts asking how important issues such as place of treatment, ability to carry on with work/normal responsibilities, fertility, and length of treatment had been. If needed, participants were reminded about the information given regarding these topics in the scenarios. Finally, all were given the opportunity to change their initial treatment preferences if they so wished.

2.3. Statistics

All data were analysed using Statistical Package for the Social Sciences (SPSS) and included Mann–Whitney U, multiple regression analyses, χ^2 and Fisher's Exact where appropriate, that is categories too small to meet the requirements for the χ^2 test.

3. Results

242 women were approached, consented and completed the study questionnaire. Of these, 30 were excluded from the analysis because they were post-menopausal ($n = 24$), had undergone a hysterectomy ($n = 4$) or did not know their menopausal status ($n = 2$). A further 12 women were excluded because of over-recruitment in certain age groups; initially, these were chosen on the basis of there being missing, but non-crucial, data from the questionnaire, then further exclusions were made randomly. This left the target sample of 200 women as outlined in Table 2, of whom 10 were peri-menopausal and the remainder pre-menopausal. Excluded women did not differ substantially from those included in the study in terms of their available demographic variables or in the pattern of their treatment choices.

3.1. Demographics of sample

Education/qualifications were categorised according to the highest level obtained. A majority (46%) of the women in our sample were educated to university degree level or higher, (27%) had 'A' levels or a professional qualification and 24% had 'O' levels/GSEs (at least

graduation from High School). Very few women (4%) had no qualifications at all. When compared with figures for women of working age provided by the Office for National Statistics [23] for the South East and the UK, a greater proportion of our sample were educated to degree level or higher and a smaller proportion had no qualifications. Carstairs deprivation scores showed that women resided in areas more affluent than the UK as a whole. However, the incidence of breast cancer varies between different socio-economic sections of the population, with the rate being approximately 30% higher in the most affluent groups compared with the most deprived [24]. Therefore, the study sample, in being relatively affluent, was more comparable to a general population of women with breast cancer in the UK.

3.2. Treatment preferences

Participants were asked for their initial treatment preference and then, after considering some issues relating to this, they were given the chance to change their mind. Table 3 shows initial and final treatment preferences. In both cases, it can be seen that significantly more women chose goserelin.

Twelve women changed their treatment preferences after considering in more detail issues to do with their choice of treatment. Seven previously undecided changed to goserelin and one undecided to chemotherapy. Two women who initially preferred goserelin became undecided and one changed to chemotherapy. One woman who initially favoured chemotherapy became undecided.

4. Factors relating to initial preferences

4.1. Place of treatment administration

There was a significant difference between the groups in terms of the importance of place of treatment (χ^2, $P < 0.0001$). Most women who chose chemotherapy thought that place of treatment was not important Fig 1. This is in contrast to the group who chose goserelin who were more likely to say that place of treatment was quite or very important.

Table 3
Initial and final treatment preferences

	Goserelin *n* (%)	Chemotherapy *n* (%)	Undecided *n* (%)	χ^2 significance
Initial	152 (76)	21 (11)	27 (14)	$P < 0.0001$
Final (12 women changed)	156 (78)	22 (11)	22 (11)	$P < 0.0001$

4.2. Ability to continue working/carry out normal responsibilities

There was a significant difference between groups ($P < 0.0001$, Fisher's Exact) in terms of how important women thought it was to be able to continue working/continue with normal responsibilities Fig 2. Most women who chose goserelin thought that being able to carry on with work/normal responsibilities during treatment was very important, whereas women who chose chemotherapy were more likely to say that it was only quite important or not important.

4.3. Fertility

There was a significant difference between groups ($P = 0.008$, Fisher's Exact) in terms of how important women thought it was to retain fertility. Over a quarter of the women who chose goserelin thought this was 'very important' in contrast to those who chose chemotherapy where no one thought this. More than half of the women in all of the groups said that retaining fertility after treatment was not important (Fig 3). To see if the importance of retaining fertility was related to age, the sample was then divided into women <40 years and those who were 40 years and over. The younger age group was significantly more likely to view the retention of fertility as important than did those aged 40 years and over (Chi Squared, $P < 0.0001$).

We also explored whether or not already having had children was related to the importance of retaining fertil-

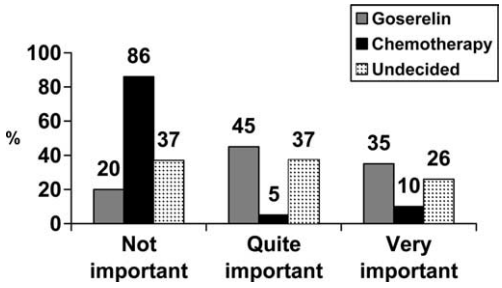

Fig. 1. The importance of the place of treatment.

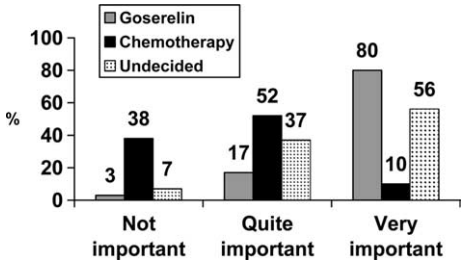

Fig. 2. The importance of being able to continue with normal responsibilities.

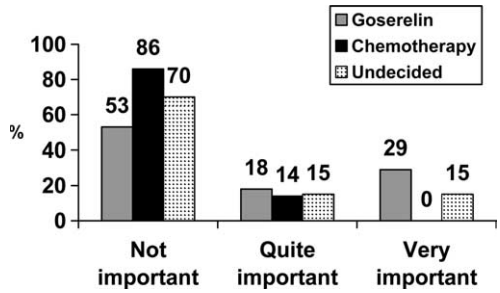

Fig. 3. The importance of retaining fertility.

ity. A significant relationship was found (χ^2; $P = 0.03$), with women who had not had children being more likely to say that retaining fertility was very important than those who already had children.

4.4. Length of treatment

There was a significant difference between groups ($P < 0.0001$; χ^2) in terms of the importance attached to the length of treatment Fig 4. Almost everyone who chose chemotherapy thought that this was 'very important', whereas nearly half of the women who chose goserelin felt the length of treatment to be unimportant. Most of the women who were undecided said that length of treatment was 'quite important'.

A multiple regression analysis was performed to establish whether or not any of the standard socio-demographic variables were related to the final treatment preference. The 22 women who were undecided about their final treatment preference were not included in this analysis. The following variables were entered into the equation: age band, Carstairs deprivation score, partnership status (has a partner versus no partner), children (has children versus no children) and education ('O' level or none versus 'A' level or professional qualification and above). None of the variables was a significant predictor of treatment preference and did not add anything over and above assuming all women would prefer goserelin.

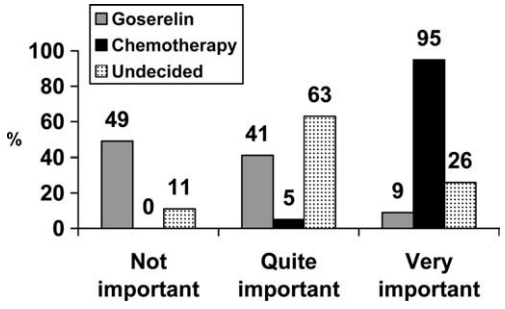

Fig. 4. The importance of length of treatment.

4.5. Impact of experience of someone close with cancer

About 131 (74%) of the women able to express a clear preference for either goserelin or chemotherapy knew of someone close with cancer. As a group, significantly more of the women with a preference for chemotherapy had personal experience of someone close with cancer (Mann–Whitney U test, $Z = -1.962$, $P = 0.05$). However, there were no differences in treatment preferences between the women who had seen someone actually go through chemotherapy and those who had not (Mann–Whitney U, $Z = -0.931$, $P = 0.352$).

4.6. Reasons for preferences

Women were all invited to write unprompted comments or reasons for their treatment preferences. These comments were then divided into different thematic categories by two raters who first coded the comments independently. Their codings were then compared and any discrepancies or ambiguities discussed until categories were agreed. Of the 152 women who initially chose goserelin, 149 women made 332 comments about their choice of treatment.

The primary reasons for the choice of goserelin Table 4 given by 71% women were to avoid the general side-effects associated with chemotherapy, in particular that of hair loss (27%). More than a third of the women also placed value on the convenience of goserelin administration, which was seen as being more likely to permit a quicker return to normality. Ability to retain fertility was cited by 17% women as a reason for their choice. The woman's age was a significant factor (χ^2; $P < 0.0001$) in whether they mentioned fertility as a reason for their choice, with more women under 40 years ($n = 18$, 40%) saying that retaining fertility had been a reason for choosing goserelin than women over 40 years ($n = 7$, 7%). We also looked at whether or not having had children was related to making a comment about the importance of retaining fertility, but it was not found to be significant. However, when we compared women who had one or no children with those who had two or more children, there was a significant difference, with more of the former group commenting that fertility had been a reason for choosing goserelin (24% versus 9.1%, $\chi^2 P = 0.01$).

Of the 21 women who initially chose chemotherapy, 20 women made 29 comments about their choice of treatment. The primary reason for choosing chemotherapy given by 95% of women and accounting for more than two-thirds of comments was that treatment could be finished more quickly.

Of the 27 women who were initially undecided, 22 women made 30 comments about being undecided.

Table 4
Reasons for goserelin preference

	Comments *N* (%)	*N* (%) women who made comment
Reasons (note some women made more than one comment)	(*n*=332)	(*n*=149)
Fewer side-effects generally and less severe	105 (32)	105 (71)
Convenience (less disruptive to life)	60 (18)	54 (36)
Avoidance of hair loss	40 (12)	40 (27)
More natural/less invasive/less toxic treatment	27 (8)	27 (18)
To maximise chance of retaining fertility	25 (8)	25 (17)
Avoidance of nausea/vomiting other gastro-intestinal effects	24 (7)	24 (16)
Avoidance of memory/concentration problems	11 (3)	11 (7)
Avoidance of fatigue	10 (3)	10 (7)
Avoidance of immune system depression	7 (2)	7 (5)
Bad reputation experiences of chemotherapy	12 (4)	12 (8)
Other	11 (3)	11 (7)
Reasons for chemotherapy preference	(*n*=29)	(*n*=20)
Convenience treatment finished quicker	19 (66)	19 (95)
Fertility not an issue	3 (10)	3 (15)
Positive experience of chemotherapy	1 (3)	1 (5)
Side effects of goserelin	4 (14)	4 (20)
Disliked idea of the injection into stomach	1 (3)	1 (5)
Other	1 (3)	1 (5)
Reasons for being undecided	(*n*=30)	(*n*=22)
Want more information/advice	16 (53)	16 (73)
Treatments seem similar	8 (27)	7 (32)
May choose neither or try alternative therapy	4 (13)	4 (18)
Worried about pre-existing medical condition or treatment	2 (7)	2 (9)

Most just wanted more information and advice (73%) before making a decision.

4.7. Comments made by women on completion of study

Several women made unprompted lengthier comments about their desire to avoid hair loss and about the perceived convenience of goserelin treatment.

Potential avoidance of hair loss and less toxicity

"*Hair loss would be particularly distressing as I would try to carry on as normal, but hair loss makes it obvious to the world that there is a medical problem*."
"*I would just hate to lose my hair, it would make me too miserable*."
"*I could not come to terms with losing my hair because I have a young child and would not want him to be affected by my physical changes*."
"*I would be able to cope more easily with the side-effects of goserelin rather than chemotherapy*."

Perceived convenience

"*goserelin appears to be less intrusive into one's life pattern*"
"*it should make it easier to carry on with normal life*"
"*less travelling to the cancer centre, simple and quick: primary care physicians are more flexible about treatment times*"

5. Discussion

The results from this study show an overwhelming preference by healthy premenopausal women for adjuvant goserelin rather than chemotherapy were they to develop early breast cancer which was oestrogen receptor-positive and there was a choice of treatments. The most common reasons for choosing goserelin were that women thought that the side-effect profile was more tolerable than for chemotherapy and that treatment by goserelin would be more convenient exerting less disruption to their lives.

A potential criticism of the present study might be that CMF chemotherapy is outdated. However, it is still in common use in many cancer centres in the UK. Over the last few years, there has been evidence suggesting that newer chemotherapy regimens containing an anthracycline are superior to CMF. The Early Breast Cancer Trialists' Collaborative Group's meta-analysis showed adjuvant therapy with anthracyclines to be 13% more effective than CMF [25]. We know that goserelin with tamoxifen is 40% more effective than CMF for recurrence-free survival [9], but there are as yet no direct comparative trials of goserelin ± tamoxifen versus anthracycline-containing chemotherapy. We also feel that presentation of information such as this to real patients facing choices in the clinic is difficult, as absolute

rather than relative benefits between treatment regimens are actually rather modest.

When comparing treatment with goserelin to chemotherapy, one of the most obvious differences is the potential effect on fertility. One might expect that goserelin would be a more attractive option to women under 40 years of age or to women who had not yet completed their families than it would be to women in their 40s and those who already had children. The results of this study were interesting and in some ways unexpected, in that there was no overall effect of age, or parity on women's treatment preferences. Although fertility was an important concern for a sub-set of the younger women who had not completed their families, only 25 (17%) gave retention of fertility as a reason for preferring goserelin.

Reasons other than fertility appeared to dominate women's preferences for goserelin. The side-effect profile of goserelin was perceived as more tolerable than that for chemotherapy. Many women specifically stated that they wished to avoid particular side-effects of chemotherapy, the primary ones being hair loss (27%) and avoidance of nausea and vomiting and other gastro-intestinal disturbances (16%). Another unexpected and more subtle theme running through the comments made by many women, was that they perceived treatment by chemotherapy to be a violent and drastic assault to the body, whereas goserelin was thought to be a gentler, more 'natural' hormone treatment (18%).

This project was conducted on a sample of women without breast cancer asked to consider the adjuvant options that might be on offer following breast cancer surgery and, as such, has all the limitations of a hypothetical study. We are also aware that there may be cultural differences with women in the UK being less enthusiastic about chemotherapy than North American women. However, several important issues emerged that merit consideration and discussion. One was that very few women had even heard of goserelin or of anyone who had ever been given it, other than a woman whose father was taking it for prostate cancer. Health-care professionals perhaps underestimate the bad reputation of, and aversion people have towards chemotherapy. Many can appear to be rather glib about hair-loss in particular, which was seen as so important to avoid by women in the study. Not all cold-cap systems are effective at reducing hair loss to a satisfactory level with all chemotherapy regimens [26] and some patients find them difficult to tolerate [27]. Furthermore, many patients find that the basic wigs supplied by the health-care providers are very uncomfortable and unattractive: a convincing and comfortable real hair wig is often quite expensive.

Another slightly surprising finding was that goserelin was seen as so much more convenient than chemotherapy in spite of the length of time that treatment takes. For busy young women, the possibility for treatment to be given by a primary care physician or community nurse was seen as a very desirable prospect, whereas trips to the cancer centre for chemotherapy would limit their opportunities to continue working and to engage in their other responsibilities, especially childcare. Only one woman said she would not have goserelin because of the injection into her abdomen.

These data demonstrate that patients may often place value on things that are not always apparent to health-care professionals. In an era when women are meant to be offered more opportunities to be partners with their health-care providers in decision-making about treatment, it is surely incumbent on physicians and specialist nurses to provide more information about all treatment options. Several authoritative bodies including the National Institute of Health (NIH) Consensus on Adjuvant Therapy [28], the St. Gallen Consensus [29] and European Society of Mastology Guidelines [30] on Endocrine Therapy, have recommended that ovarian oblation with luteinising hormone-releasing hormone (LHRH) agonists in combination with tamoxifen should be made available to pre-menopausal women with ER-positive tumours, but these guidelines have not been widely accepted. The numbers of women who genuinely gain extra disease-free life from adjuvant treatment is small, thus many will experience side-effects that have a deleterious impact on their quality of life. Women should be provided with more realistic appraisals of the true gains and pains associated with adjuvant treatment.

Conflict of Interest

None declared for any authors.

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