**Name of Journal: *World Journal of Hepatology***

**ESPS Manuscript Number: 21181**

**Manuscript Type: MINIREVIEWS**

**Psychosocial assessment and monitoring in the new era of non-interferon-alpha hepatitis C virus** **treatments**

Rowan PJ *et al.* Psychosocial assessment and non-interferon-alpha HCV treatments

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**Author contributions:** Dr. Rowan conceived the study plan, identified data sources, analyzed data, drafted the manuscript, and approved the final version; Dr. Bhulani sought and identified relevant data for analysis per plan, contributed to analysis of data, contributed to drafting the manuscript, and approved the final version.

**Conflict-of-interest** **statement:** The authors have no conflicts of interest.

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**Received:** June 30, 2015

**Peer-review started:** July 5, 2015

**First decision:** July 31, 2015

**Revised:** August 7, 2015

**Accepted:** August 30, 2015

**Article in press:**

**Published online:**

**Abstract**

**Chronic hepatitis C virus (HCV) is a global concern.** With the 2014 Food and Drug Administration (FDA) approvals of two direct-acting antiviral (DAA) regimens, ledipasvir/sofosbuvir regimen and the ombitasvir/paritaprevir/ritonavir and dasabuvir regimen, we may now be in the era of all-pill regimens for HCV. Until this development, i**nterferon-alpha along with Ribavirin has remained part of the standard of care for HCV patients. That regimen necessitates psychosocial assessment of factors affecting treatment eligibility, including interferon-alpha-related depressive symptoms, confounding psychiatric conditions, and social aspects such as homelessness affecting treatment eligibility. These factors have delayed as much as 70% of otherwise eligible candidates from interferon-based treatment, and have required treating physicians to monitor psychiatric as well as medical side effects throughout treatment. All-pill DAA regimens with the efficaciousness that would preclude reliance upon interferon-alpha or ribavirin have been anticipated for years. Efficacy studies for these recently approved DAA regimens provide evidence to assess the degree that psychosocial assessment and monitoring will be required. With shorter treatment timelines, greatly reduced side effect profiles, and easier regimens, psychosocial contraindications are greatly reduced. However, current or recent psychiatric comorbidity, and drug-drug interactions with psychiatric drugs, will require some level of clinical attention. Evidence from these efficacy studies tentatively demonstrate that the era of needing significant psychosocial assessment and monitoring may be at an end, as long as a manageable handful of clinical issues are managed.**

**Key words: Depression; Therapy; Psychiatry; Clinical; Direct-acting antivirals**

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**Core Tip:** The recently Food and Drug Administration approved direct-acting antiviral (DAA) regimens for **hepatitis C virus (HCV)**, ledipasvir/sofosbuvir regimen and the ombitasvir/paritaprevir/ritonavir and dasabuvir regimen, have demonstrated great efficacy, and thus far seem to have short treatment timelines and relatively benign side effect profiles. Depression has not emerged as a side effect of these treatments. With efficacious regimens that include no interferon-alpha and no ribavirin, there may no longer be a need for strong psychosocial assessment and monitoring built into the routine of HCV treatment. Good history-taking, strong pharmaceutical review, and reliable consultative relationships should be adequate for meeting psychosocial needs in HCV treatment.

Rowan PJ, Bhulani N. Psychosocial assessment and monitoring in the new era of non-interferon-alpha **hepatitis C virus** treatments. *World J Hepatol* 2015; In press

**Introduction**

**Chronic hepatitis C Virus (HCV) is a global concern, with approximately 170 million people affected worldwide. It is the leading cause of liver cirrhosis in developed countries[1,2]. Of the 6 genotypes, genotype 1 is the most prevalent[3]. Interferon alpha was recognized as a successful treatment in the 1980s, but success rates were low. Since 1998, Interferon-alpha along with ribavirin has remained the standard of care for HCV infected patients, with success rates in genotype 1 only at approximately 40%, while success rates for genotypes 2 and 3 hover around 80%. Until recently, the only significant change to this regimen was the approval of pegylated interferon-alpha treatment, in 2001, making the regimen less challenging by reducing injections per week and boosting efficacy to some degree.**

**Due to side effects of this regimen, candidates must be assessed for eligibility. A**s much as 70% of otherwise eligible patients are not eligible to begin treatment due to contraindications[4,5]. A leading contraindication has been depression, since a leading side effect is the depression that may emerge or be exacerbated by interferon-alpha. Clinicians have also had to monitor other psychosocial issues, such as substance abuse. Some evidence suggests that treatment does not seem to work in active alcohol users[6], although some assessment have shown similarly successful outcomes regardless of current alcohol abuse[7]. Injection drug users have been perceived as at risk for insufficient adherence[8], and also at risk for re-infection[9], so thisposes another area of psychosocial assessment. Clinically, a common practice has been to refer an otherwise eligible candidate for psychiatric care when any of these psychiatric conditions are present or have been recently active.

Another psychosocial concern is social stability: since treatment may take as long as 48 wk, a candidate must have stable housing and have means for refrigerating the interferon-alpha. Those with unstable housing or unstable income might need to have those issues addressed by social work before treatment can be initiated. For women of child-bearing age, the teratogenic risk of ribavirin requires attention to pregnancy risk. A recommended practice has been to assure mandatory birth control adherence for any woman of child-bearing age to be prescribed any extended regimen that includes ribavirin[10]. Thus, while the prevailing regimen promises good outcomes for many, psychosocial assessment and monitoring has been a necessary part of HCV treatment.

**Major changes to this clinical picture began in 2011, with approval of the first direct-acting antivirals (DAA), boceprevir and teleprevir. While these drugs greatly boosted genotype-1 success rates and shortened treatment time by months, these successes were gained by augmenting an interferon-alpha and ribavirin regimen with these newer drugs. So, patients still faced the side effects and contraindications associated with interferon-alpha and with ribavirin.**

With the 2014 Food and Drug Administration (FDA) approvals of the ledipasvir/sofosbuvir “Harvoni” regimen and the ombitasvir/paritaprevir/ritonavir and dasabuvir “Veikira Pak” regimen, and with more regimens under development, we may now be in the era of all-pill regimens for HCV. Compared to the prevailing standard of interferon-alpha-plus-ribavirin regimen that has prevailed since the 1990s, this advancement in HCV treatment is revolutionary for a few reasons: these new regimens have superior efficacy across genotypes; the treatment timeline is relatively brief; and patients no longer need to self-administer a medication by injection. Also, a further advancement seems to be the favorable side effect profile.

Clinics treating HCV patients have had to develop the capacity to provide the noted psychosocial assessment and monitoring. With the advent of these new regimens, it is worth reviewing their side effect profiles to consider the degree that psychosocial assessment and monitoring will continue to be part of HCV treatment. This requires examining how lengthy and complex any regimen is, the rates of discontinuation, the degree of psychiatric adverse events experienced by study enrollees, and whether any regimen medications have any psychosocial contraindications (*e.g.*, homelessness, risk of pregnancy). This review draws upon previously published data, and no original data, so no institutional review board approval was needed, and no consenting of any participants was required; it is also noted that the authors have no conflicts of interest.

***Ledipasvir-sofosbuvir regimen: Psychosocial aspects***

The ledipasvir-sofosbuvir regimen, commercially available as Harvoni®, received FDA approval on October 10, 2014. The ION series of studies[11] established safety and efficacy for this regimen. ION-1 allowed individuals with mental illness to enroll, as long as the condition had been well-controlled for at least a year. Also, exclusion criteria included those with any psychiatric hospitalization, suicide attempt, or psychiatric disability period in the recent five years (ION-1 Study Protocol, 4.3 g). A positive drug screen, elevated AUDIT (excessive-alcohol screener) score, or drug abuse in the recent 12 mo were also exclusionary criteria. Therefore, enrollees could have a mental illness such as depression, but had to be free from recent complications of that condition. In the ION-1 study, there was no drop-out due to side effects (one enrolled participant dropped out after only one dose), and only 4 of the 431 participants receiving the ledipasvir-sofosbuvir regimen regimen were lost to follow-up: loss to follow-up can reflect any of many factors, including a passive refusal to continue a regimen due to side effects or a regimen that is too complex. This rate of loss to follow-up is much lower than interferon-based trials. In the initial study providing the superiority of pegylated interferon, by Fried and colleagues[12], 677 participants were randomized and began treatment in the two pegylated interferon arms (one with ribavirin, one with placebo); of these, 145 (21.4%) experienced depression, and 28 (4.1%) discontinued treatment (20 refused to continue treatment at some point after beginning, and 8 had failure to return). About the same time, a similar efficacy study of pegylated interferon-alpha was conducted by Manns and colleagues[13]. In this study, 30% of the 1025 patients in the two study arms receiving pegylated interferon-alpha experienced depression symptoms. In another analyses of these data[14], the researchers noted that 218 of 1010 (21.6%) patients receiving interferon-alpha sustained treatment for less than 80% of the planned treatment time span. Thus, depressive side effects and other aspects of interferon-based regimens have been challenging for patients to tolerate. For the ledipasvir-sofosbuvir regimen, low rates of discontinuation may also be due to the ease of compliance with the regimen: both medications are combined in one pill, taken orally once daily.

In the ION-1 trial, no psychiatric serious adverse events were reported among participants taking the ledipasvir-sofosbuvir regimen, although other serious adverse events, such as chest pain and pneumonia, occurred in a few of these patients. Thus, overall, there does not yet seem to be any notable risk of psychiatric symptomatology for the ledipasvir-sofosbuvir regimen, per study adverse event reporting or as might be suggested by drop-out/loss to follow-up or by adherence data. These study data indicate that, so far, psychiatric problems such as depressive symptoms do not seem to be a side effect of treatment, although it must be acknowledged that study criteria excluded those with current or recent psychiatric difficulty.

A related study, ION-3, was conducted to determine whether a more brief regimen, 8 weeks versus 12 of ledipasvir-sofosbuvir, could be as efficacious[15]. This study, with a protocol largely parallel to ION-1, included 215 participants in the 8 wk ledipasvir-sofosbuvir arm and 216 in the 12 wk arm. Among these participants, the study’s Supplementary Materials indicate no psychiatric adverse events, and report very low rates of drop-out/loss-to-follow-up (4 of 431; 0.9%). So, again, the ledipasvir-sofosbuvir regimen seems very unlikely to produce psychiatric adverse events, or to have treatment discontinuation.

Is pregnancy risk a concern for the ledipasvir-sofosbuvir regimen, as for the interferon-alpha/ribavirin regimen? Thorough data, such as a randomized clinical trial with pregnant women, have not been conducted, and post-marketing surveillance is still young, so human data are limited. The FDA-approved medication insert data report that animal-model studies have failed to find any teratogenic effect when given to rats or rabbits at exposures that are 3 or more times greater than human doses. The status for pregnant women is currently Category B: a**nimal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.**

**Does the** ledipasvir-sofosbuvir regimen have contraindications with any psychiatric medications, requiring close scrutiny in patients prescribed psychiatric medications? Prescribing information report no such noted conflicts, and neither of the two component medications have metabolism by CYP cytochromes, a common biological indicator of possible drug-drug difficulties for psychiatric medications. Post-marketing surveillance has been brief, but thus far contraindications for psychiatric medications have not been detected for this regimen.

***Ombitasvir-paritaprevir-ritonavir and dasabuvir: Psychosocial aspects***

Ombitasvir-paritaprevir-ritonavir plus dasabuvir is commercially available as Viekira Pak®, which is a once daily pill of ombitasvir-paritaprevir-ritonavir and a twice daily pill of dasabuvir[16]. Two related studies with similar potocols, PEARL-III and PEARL-IV[16], assessed the efficacy and adverse events of this regimen. Each studied the ombitasvir-paritaprevir-ritonavir plus dasabuvir regimen with or without ribavirin in randomized, placebo-controlled trials. PEARL-IV studied patients with genotype 1a, and PEARL-III studied those with genotype 1b. The placebo arms (no ribavirin) of each of these studies provide relevant data regarding possible psychosocial issues to be assessed and monitored in this no-interferon-alpha, no-ribavirin regimen.

Potential participants with current or recent alcohol or substance abuse (recent 6 mo) were excluded, but otherwise psychiatric comorbidity was not an exclusion. Together, in the placebo arms (no ribavirin), there were 414 participants who participated in 12 wk treatment. Aside from those discontinuing treatment due to virologic failure or to adverse events that had no psychosocial aspect, there were only 6 (1.4%) who did not complete treatment (consent withdrawn, lost to follow-up, or “other” reason). As noted earlier, reason for loss to follow-up cannot be ascertained, but it must be considered that psychiatric side effects or adverse events could be involved. These rates of non-completion are far lower than the rates, noted earlier, for interferon-alpha regimens.

The Supplementary Materials for PEARL-III and IV note adverse events, reported per Medical Dictionary for Regulatory Activities (MEDDRA) vocabulary. No distinctly psychiatric adverse events are noted except for “memory impairment”, reported by 14 (3.3%) of participants in the no-ribavirin arms of these studies.

So, the ombitasvir-paritaprevir-ritonavir plus dasabuvir regimen seems to be well-tolerated, with strong compliance and a very small burden of psychiatric side effects. Substance abuse may reasonably be a contraindication; more data are likely needed on the degree that those with current or recent psychiatric difficulties may need to be delayed from treatment, but this regimen seems to hold promise for those with psychiatric comorbidities.

There are two well-recognized psychosocial issues with this regimen: the inclusion of ritonavir is problematic for women of reproductive age, and there is a long list of drug-drug interactions between ritonavir and other medications, including several medications used for psychiatric indications. These challenges arise mainly because ritonavir inhibits the liver enzyme cytochrome P450-3A4[17], and so affects to some degree the pharmacokinetics of any drug affected by this enzyme. Extensive data exist regarding pharmacology of ritonavir because it has been recognized for years as part of efficacious HIV treatment[18]. Also, the University of California San Francisco “HIVInsite” website[19] has extensive data on HIV/AIDS drugs, including ritonavir, and is the source of some of the following observations regarding drug-drug interactions.

Ritonavir reduces the efficacy of hormone-based birth control[20,21]. The PEARL study protocols have required that women participating in the trials avoid pregnancy by using at least two forms of birth control, neither of which can be hormone-based. So, along with recognized evaluation for HCV treatment, providers will need to assess and monitor pregnancy risk, and pregnancy prophylaxis, for women of reproductive age.

Many of the ritonavir drug-drug interactions are with medications that have psychiatric indications, including carbamazepine (bipolar disorder), nefazodone (depression), and triazolam (insomnia). So, assessment and monitoring will require surveillance of psychiatric conditions and any medications for these. It is possible that patients taking triazolam for insomnia may not perceive themselves as having a “psychiatric” condition, so merely asking about “psychiatric” diagnoses or prescriptions may not reveal that a patient is using this drug; as is generally advisable, patients should be encouraged to report any and all prescription drugs, as well as over-the-counter drugs and any herbal or “alternative” remedies. Regarding herbal/alternative drugs, patients should avoid taking both ritonavir and John’s Wort[21], a fairly commonly utilized herbal remedy for depression. Ritonavir also has a drug-drug interaction with sildenafil, used for erectile dysfunction; use of both drugs can lead to pulmonary arterial hypotension, and there are drug-drug interactions with other drugs used for erectile dysfunction as well, including avanafil, tadalafil, and vardenafil. There is a fair amount of clinical folklore and evidence that sildenafil is misused for recreational purposes[22,23], so the clinical management of HCV treatment that includes ritonavir must assess and monitor the use of erectile dysfunction drugs, whether this use is legitimate use or recreational use.

 In conclusion, clinical trial data indicate that these recently approved, all-pill, no-interferon-alpha/no ribavirin regimens are far more readily tolerated by patients generally, and do not seem to have notable psychiatric contraindications. Challenges of these regimens may be limited to examining drug-drug interactions, including the prescription of drugs for psychiatric indications or for birth control. None of these issues requires significant involvement of specialty mental health or social work professionals, although it is necessary to have these services readily available by consultation.

The type of psychosocial assessment and monitoring required for these regimens is typical in medical care delivery, and the adoption of the electronic medical record and e-prescribing can support the detection of potential drug-drug interactions. In many cases, precautions or alternative clinical management strategies can be determined for the duration of the 12 wk treatment, in consultation with a pharmacist, the prescriber overseeing the psychiatric condition, or both. So, with these recently FDA-approved DAA regimens for HCV, with no interferon-alpha and no ribavirin, treatment settings may no longer need to have strong psychosocial assessment and monitoring built into the routine of HCV treatment.

There are some further research issues to be assessed for these recently-approved DAA regimens. As clinical experience builds with all-pill DAA regimens, the experience of patients with well-controlled or poorly-controlled psychiatric comorbidity should be noted and reported. One or both of these regimens may be well-tolerated in patients with a range of psychiatric comorbidities. If the DAA regimens are well-tolerated by those with current or recent psychiatric comorbidities, this would greatly broaden the range of patients eligible to initiate therapy. Also, it would be valuable to investigate patient preferences for avoiding pregnancy for the duration of treatment. As evidence builds, we will be able to more firmly determine whether we have entered an era in which there is no longer any great need for psychosocial assessment and monitoring of patients undergoing HCV treatment.

**REFERENCES**

1 **GBD 2013 Mortality and Causes of Death Collaborators**. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**: 117-171 [PMID: 25530442 DOI: 10.1016/S0140-6736(14)61682-2]

2 **Dienstag JL**, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. *Gastroenterology* 2006; **130**: 231-64; quiz 214-7 [PMID: 16401486 DOI: 10.1053/j.gastro.2005.11.010]

3 EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; **55**: 245-264 [PMID: 21371579 DOI: 10.1016/j.jhep.2011.02.023.]

4 **Talal AH**, LaFleur J, Hoop R, Pandya P, Martin P, Jacobson I, Han J, Korner EJ. Absolute and relative contraindications to pegylated-interferon or ribavirin in the US general patient population with chronic hepatitis C: results from a US database of over 45000 HCV-infected, evaluated patients. *Aliment Pharmacol Ther* 2013; **37**: 473-481 [PMID: 23289640 DOI: 10.1111/apt.12200]

5 **Rowan PJ**, Tabasi S, Abdul-Latif M, Kunik ME, El-Serag HB. Psychosocial factors are the most common contraindications for antiviral therapy at initial evaluation in veterans with chronic hepatitis C. *J Clin Gastroenterol* 2004; **38**: 530-534 [PMID: 15220690 DOI: 10.1097/01.mcg.0000123203.36471.70]

6 **Weber KT**, Janicki JS, Reeves RC, Hefner LL. Factors influencing left ventricular shortening in isolated canine heart. *Am J Physiol* 1976; **230**: 419-426 [PMID: 1259023]

7 **Bruggmann P**, Dampz M, Gerlach T, Kravecz L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. *Drug Alcohol Depend* 2010; **110**: 167-171 [PMID: 20334985 DOI: 10.1016/j.drugalcdep.2010.02.016]

8 **Aspinall EJ**, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, Goldberg DJ, Hellard ME. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis* 2013; **57** Suppl 2: S80-S89 [PMID: 23884071 DOI: 10.1093/cid/cit306]

9 **Micallef JM**, Macdonald V, Jauncey M, Amin J, Rawlinson W, van Beek I, Kaldor JM, White PA, Dore GJ. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *J Viral Hepat* 2007; **14**: 413-418 [PMID: 17501762 DOI: 10.1111/j.1365-2893.2006.00812.x]

10 **Hoofnagle JH**, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med* 2006; **355**: 2444-2451 [PMID: 17151366 DOI: 10.1056/NEJMct061675]

11 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]

12 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982 [PMID: 12324553 DOI: 10.1056/NEJMoa020047]

13 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965 [PMID: 11583749 DOI: 10.1016/S0140-6736(01)06102-5]

14 **McHutchison JG**, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J, Lee WM, Mak C, Garaud JJ, Albrecht JK. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002; **123**: 1061-1069 [PMID: 12360468 DOI: 10.1053/gast.2002.35950]

15 **Kowdley KV**, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herring R, Di Bisceglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; **370**: 1879-1888 [PMID: 24720702 DOI: 10.1056/NEJMoa1402355]

16 **Ferenci P**, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Janczewska E, Rizzardini G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014; **370**: 1983-1992 [PMID: 24795200 DOI: 10.1056/NEJMoa1402338]

17 **Zeldin RK**, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. *J Antimicrob Chemother* 2004; **53**: 4-9 [PMID: 14657084 DOI: 10.1093/jac/dkh029]

18 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. [accessed 2015 Jun 15]. Available from: URL: http: //www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL. pdf.

19 University of California at San Francisco HIV/AIDS Division. HIVInsite Gateway. [accessed 2015 Jun 15]. Available from: URL: http: //hivinsite.ucsf.edu/InSite

20 **El-Ibiary SY**, Cocohoba JM. Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives. *Eur J Contracept Reprod Health Care* 2008; **13**: 123-132 [PMID: 18465473 DOI: 10.1080/13625180701829952]

21 **Ouellet D**, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, Leonard JM, Granneman GR. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998; **46**: 111-116 [PMID: 9723818 DOI: 10.1038/clpt.2009.206]

22 **Smith KM**, Romanelli F. Recreational use and misuse of phosphodiesterase 5 inhibitors. *J Am Pharm Assoc (2003)*; **45**: 63-72; quiz 73-5 [PMID: 15730119 DOI: 10.1331/1544345052843165]

23 **Apodaca TR**, Moser NC. The use and abuse of prescription medication to facilitate or enhance sexual behavior among adolescents. *Clin Pharmacol Ther* 2011; **89**: 22-24 [PMID: 21170066 DOI: 10.1038/clpt.2010.264]

**P-Reviewer:** Garcia-Elorriaga G, Isamu S **S-Editor:** Qiu S **L-Editor: E-Editor:**