Guidelines for the Treatment of Hepatitis C Virus Infection in Injection Drug Users: Status Quo in the European Union Countries

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Treatment guidelines are considered to be an important tool in steering patients to medical treatment. This study was conducted to analyze guidelines for the treatment of hepatitis C virus (HCV) infection in injection drug users (IDUs) in the European Union (EU) countries as a component of treatment access. National and international databases, expert contacts, professional societies, and health administrations were approached to acquire guidelines. According to their quality standard, guidelines were divided into expert opinions, semiofficial guidelines, official guidelines, and consensus processes. Recommendations for the treatment of HCV infection in IDUs vary substantially, from lack of recommendations and outright treatment disapproval to recommendations for treatment under specified circumstances. Recent guidelines that apply qualified process procedures that include literature research tend to be more permissive. Qualified guideline processes in each EU country and subsequently renewed pan-European guidelines are needed.

Chronic infection with hepatitis C virus (HCV) is considered to be a major burden, both to those infected and to the public health system [1]. Besides alcoholism, chronic HCV infection is the major cause of liver cirrhosis and end-stage liver disease and the main reason for liver transplantation [2]. Moreover, chronic HCV infection is associated with increased rates of depression and fatigue and leads to impaired quality of life [3, 4]. The future health costs in 10 European Union (EU) countries for 1 year of drug-related HCV, hepatitis B virus, and HIV infection were estimated at €1.89 billion, with HCV accounting for nearly 40% [5]. Within the EU countries, the prevalence of HCV infection in the general population is as high as 3%; among injection drug users (IDUs), the prevalence of HCV infection is 30%–98% [6–8]. The introduction of antiviral combination therapy with ribavirin and pegylated IFN has led to sustained virological response in >50% of patients; however, rates depend on the HCV genotype [9, 10]. Nevertheless, treatment of HCV infection in IDUs is still the subject of controversy. Reasons for withholding antiviral therapy from IDUs may include the assumption of poor adherence, fear of adverse effects, and the risk of reinfection [11]. There is evidence that IDUs can adhere to medical protocols in the same manner as do non-IDUs [12], and early pilot studies showed that antiviral treatment of chronic HCV infection in IDUs is both safe and effective [13–17]. Rates of reinfection in IDUs may not necessarily be higher than in non-IDU populations [18]. Despite these promising results, IDUs may face barriers when trying to gain access to treatment for chronic HCV infection. Treatment guidelines have an increasing effect on the provision of therapies, because, in times of limited resources, allocation of even these limited resources follows, among other considerations, the recommendations of guidelines. In addition, treatment guidelines may have an effect on the provision of qualifications

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for professionals and on the willingness of sponsors to pay for treatment and of professionals to provide treatment [19, 20]. This study was undertaken to analyze guidelines for the treatment of HCV infection as applied in the EU countries with regard to treatment accessibility for IDUs.

METHODS

Guidelines for the treatment of HCV infection were retrieved by researching international databases and requesting information from professional societies and experts. The MEDLINE database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) was used with the keywords "guidelines," "management," "guidance," and "treatment"—in combination with the terms "hepatitis," "hepatitis C," and "HCV." The first 200 publications that were presented for each keyword were considered. Publications from non-EU countries except for Norway were not taken into account. Authors of relevant references were screened for further publications about these topics. Internet home pages of international and national professional societies in the areas of addiction medicine, gastroenterology, and hepatology were screened for guidelines and experts. Experts, as identified by the European Monitoring Centre for Drugs and Drug Addiction (http://www.emcdda.eu.int) and the Centre for Interdisciplinary Addiction Research of the University of Hamburg (http://www.zis-hamburg.de), were asked to provide both guidelines and expert contacts in their country. In addition, we contacted experts and/or institutions discovered via the European Society for the Study of the Liver (EASL; http://www.easl.ch), European Network for HIV/AIDS and Hepatitis Prevention in Prisons, and European Information Network on Drugs and Drug Addiction (http://www.emcdda.eu.int/index.cfm?fuseaction=public.Content&nNodeID=403&sLanguageISO=EN). To assess quality levels, guidelines were divided into consensus papers, official guidelines, semiofficial guidelines, and expert opinions. To qualify as a consensus paper, guidelines had to follow, at least partially, recommendations for development in the areas "scope and purpose," "stakeholder involvement," "rigor of development," "clarity of presentation," "applicability," and "editorial independence," as suggested by the Appraisal of Guidelines Research and Evaluation collaboration [21]. To qualify as official guidelines, guidelines had to be authored by a professional organization; to qualify as semiofficial guidelines, the authorship of at least 3 experts on the topic was required. Recommendations by single experts on the topic were rated as expert opinions.

RESULTS

The results of this research are presented by country, guideline quality level, and content analysis.

EU. The latest consensus paper of the EASL was published in 1999. It states that "Active intravenous drug users should not be treated due to the risk of reinfection. In addition, compliance with treatment is poor in patients in whom alcoholism has not been interrupted and in whom drug addiction continues" [22, p. 958].

Austria. The Austrian Society of Gastroenterology and Hepatology published in 1998 official guidelines for the treatment of viral hepatitis. This publication states, "For persons actively injecting drugs and/or drinking alcohol antiviral treatment is absolutely contraindicated. Patients after successful detoxification and/or patients in methadone maintenance therapy may receive antiviral treatment" [23, p. 25]. A group of 7 authors who are specialists in addiction medicine published guidelines for treatment of chronic hepatitis C in drug users in Austria from the point of view of addiction medicine, which was categorized as semiofficial guidelines [24]. These authors indicate that patients are eligible for treatment after at least 6 months of abstinence or, in case of substitution treatment, without additional drug use or, in case of drug use, no injection drug use or intoxication and few psychosocial deficits. Patients definitely not eligible for treatment are characterized by periodically or continuously uncontrolled drug use or by injection drug use without applying safer-use criteria. Patients undergoing substitution treatment who follow safer-use criteria when injecting intravenously or IDUs who follow safer-use criteria are possibly eligible for treatment. Recently, Ferenci [25] published his expert opinion, which is largely in concordance with the 1998 recommendations of the Austrian Society for Gastroenterology and Hepatology.

Belgium. The Steering Committee of the Belgian Association for the Study of the Liver published official guidelines [26]; however, these guidelines lack recommendations for patients with drug-related problems. A group of 4 authors published guidelines categorized as semiofficial, which stated that "…current studies support that the anti-HCV therapy of IVDUs [IDUs] should be the same as in other HCV-infected patients" but excluded certain IDUs by saying that "Patients with uncontrolled active intravenous drug use are not candidates for medical treatment due to lack of compliance and a high risk of re-infection" [27, p. 99].

Denmark. One expert opinion was acquired in Denmark. It was reported that most Danish treatment centers adhere to the EASL consensus report. "[Being an] IDU is not a reason for exclusion and certainly substitution treatment is not. Most centres would however not treat IDUs actively injecting" (B. P. Christensen, personal communication).

Finland. Two semiofficial guidelines were acquired for Finland. In the guidelines from the year 2002 it is assumed that IDUs "…even if drug dependence does not exist any longer, cannot profit from therapy" [28, p. 1261]. The other guidelines, published in 2003, states that "…long-term intravenous drug

consumption…represents a clear contra-indication of therapy…" [29, p. 525].

France. The French consensus paper states that "occasional intravenous drug use by an otherwise stabilized patient does not contraindicate treatment" [30, p. 306]. Expert opinions and literature research constituted an integral component of the consensus process. An expert mapped out that a nonstabilized IDU with ongoing drug use must not be treated [31]; on behalf of the bibliographic group, a case-by-case decision was recommended [32].

Germany. One official guidelines and 2 semiofficial guidelines exist. The author of the official guidelines is the German Society of Digestive and Metabolic Diseases. This publication states that "an interferon-based therapy should not be initiated in active drug and/or alcohol users. Drug users should be abstinent before initiation of interferon-based therapy for at least twelve months, alcoholics for at least six months. No consensus exists as to treatment of patients in methadone maintenance programs" [33, p. 981]. Semiofficial guidelines authored by the president of the German Society of Addiction Medicine recommends postponing treatment in cases of <12 months of abstinence in drug users or in cases of substantial alcohol intake [34]. A second semiofficial guidelines was authored by 8 experts on the topic under the auspices of the German Ministry of Health and the Robert Koch Institute. This publication recommends treatment of IDUs within a methadone maintenance program, restricts treatment of IDUs after detoxification to specialized centers, and recommends treatment of abstinent IDUs in general in close collaboration with experts in addiction medicine (U. Marcus, Ministry of Health and Social Security, personal communication).

Greece. No data were acquired.

Ireland. No data were acquired.

Italy. An expert on the topic stated that there are no specific guidelines for the treatment of HCV infection in IDUs (G. Rezza, personal communication). Guidelines of the Italian Association for the Study of the Liver will be published soon (M. Strazzabosco, personal communication).

Luxembourg. No data were acquired.

The Netherlands. According to an expert opinion, treatment for HCV infection is offered to IDUs within a special treatment program [35], although inclusion criteria remain unclear.

Norway. According to guidelines classified as semiofficial, "Patients addicted to alcohol should not be treated. The same applies to those addicted to other substances, although heroin addicted sometimes are successfully treated. Drug addicts treated with methadone are in exceptional cases also treated with IFN and ribavirin. Until now, six months abstinence before initiating HCV-therapy has been required" [36, p. 927].

Portugal. No data could be acquired.

Spain. Two official guidelines, authored by the Spanish College of Hospital Pharmacists and the Society of Primary Care Physicians, respectively, do not address the problem of treatment for HCV infection in IDUs [37, 38]. Two semiofficial guidelines, each authored by a group of 6 experts, do not consider injection drug use as a treatment contraindication [39, 40]. An expert opinion promoted by the Spanish Association for the Study of the Liver (http://www.aeeh.org) does not specifically address the topic of treatment of HCV among IDUs. On this Web page, consensus papers of the National Institutes of Health [41] and the EASL [22] are also presented. Therefore, the official position of this professional society remains unclear. In the autonomous region of Catalonia, official guidelines published by the Department of Health and Social Security [42] considers injection drug use a contraindication for the treatment of HCV infection.

Sweden. Official guidelines authored by 19 experts considers "ongoing or recent drug or alcohol abuse" a contraindication for treatment [43]. The official guidelines of the Swedish Medical Products Agency considers "ongoing or recent drug use" a relative contraindication for treatment [44].

United Kingdom. The official guidelines of the Royal College of Physicians of London and the British Society of Gastroenterology states that "current IVDUs should not be treated although in selected cases ex-IVDUs taking regular oral methadone may be considered for treatment" [45, p. i7]. The official guidelines of the National Institute for Clinical Excellence states that "treatment of people who continue to use drugs intravenously is often not indicated due to the high probability of reinfection, presumed likelihood of relatively high levels of noncompliance and the possibility of drug interactions. Cessation of intravenous drug use before starting antiviral treatment is therefore important. Combination therapy is not contra-indicated for former intravenous drug users whose drug use has been stabilized on oral methadone or other products such as buprenorphine" [46].

Scotland. The official guidelines of the Scottish Executive states that "treatment is not recommended for drug users who continue to inject, where drug interactions, compliance and the possibility of reinfection are issues. This will need to be assessed on a case-by-case basis" [47, p. 7]. Table 1 encapsulates the findings described above.

CONCLUSION

This study was conducted to provide an overview on the guidelines for treatment of chronic HCV infection in IDUs. Because of the disabling potential of HCV infection and its high prevalence among IDUs, it is considered to be a major burden to both the public and the individual. Treatment guidelines have an effect of allocation of resources and provision of therapy in terms of finances, qualification, and outreach. Therefore, treat-

Table 1. Guidelines for treatment of hepatitis C infection in the European Union countries and Norway.

Country (year of publication)	Quality standard				Treatment recommendation				
	Expert opinion	Semiofficial guideline	Official guideline	Consensus paper	NR	Abstinence for ⩾6–12 months	Abstinence	Methadone maintenance treatment	Injection drug use no contraindication[a]
EU (1999)				X			X		
Austria (1998)			X				X	X	
Belgium (2003)			X		X				
Denmark (2003)	X						X		
Finland (2003)		X					X	X	
France (2002)				X					X
Germany (1997)			X			X			
Greece	Unk								
Ireland	Unk								
Italy (2003)	X				X				
Luxembourg	Unk								
The Netherlands (2002)	X				Unk				
Norway (2002)		X				X			
Portugal	Unk								
Spain (2001)			X		X				
Catalonia (2003)			X				X		
Sweden (2003)			X				X		
United Kingdom (2000)			X				X	X	
Scotland (2000)			X				X		

NOTE. Under "quality standard," only the guideline with the highest quality level for the respective country was considered. EU, European Union; NR, no recommendation; Unk, unknown.

[a] Under specific circumstances.

ment access is influenced by guidelines. Treatment guidelines allowing for or even recommending treatment of a specific disease can facilitate access to treatment [19, 20].

Data were gathered in Austria, Belgium, Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Spain including Catalonia, Sweden, and the United Kingdom (including Scotland). Contacts were established in Greece, Ireland, Luxembourg, and Portugal as well, but data quality and sources remain unclear yet and are therefore not considered. According to their quality level, guidelines were categorized into expert opinions, semiofficial guidelines, official guidelines, and consensus papers (table 1). Taking into account only guidelines with the highest level, the EU and French guidelines met criteria of consensus papers; in Austria, Belgium, Germany, Spain (including the autonomous region of Catalonia), Sweden, and the United Kingdom (including Scotland), guidelines met the criteria of official guidelines; semiofficial guidelines were found for Finland and Norway; and expert opinions were retrieved in Denmark (P. Christensen, personal communication), Italy (M. Strazzabosco and G. Rezza, personal communications), and The Netherlands [22, 23, 26, 28, 29, 30, 33, 36, 41–43, 45–47]. Treatment of HCV infection in active IDUs is allowed under specific circumstances according to the French consensus; methadone maintenance was regarded as a treatment requirement by the official guidelines of Austria and the United Kingdom and the expert opinion from Finland (M. Färkkilä and H. Nuutinen, personal communication) [23, 30, 45, 46]. Abstinence was a pretreatment prerequisite in the EU consensus, in the official guidelines of Germany, Sweden, Scotland, and Catalonia, in the semiofficial guidelines of Finland and Norway, and in the expert opinion of Denmark (P. B. Christensen, personal communication) [22, 28, 29, 33, 36, 42, 43, 47]. Treatment recommendations were lacking in the official guidelines from Belgium and Spain as well as in the expert opinion from Italy (M. Strazzabosco and G. Rezza, personal communications) [26, 41]. Treatment recommendations remain unclear in the expert opinion from The Netherlands [35]. Publication dates of guidelines vary from 1997 to 2003 and therefore cannot consider the evidence published thereafter. Besides mentioned guidelines which qualify for the highest level of quality in the respective country, additional and more recent guidelines with a lower level of quality exist in Austria, Belgium, Germany, and Spain. Two of these guidelines [25, 34] are as restrictive as and 5 are more permissive than the older and higher-level guidelines in the respective country (U. Marcus, personal communication) [24, 27, 39, 40]. Overall, treatment guidelines qualifying for a higher quality level and/or published more recently are more likely to allow for treatment of IDUs under specific conditions

and/or under methadone maintenance therapy (U. Marcus, personal communication) [24, 27, 30, 39, 40]. First clinical studies showing that treatment of HCV infection in IDUs is as safe and effective as in non-IDUs [13–17] and that rates of reinfection are not necessarily higher than in non-IDU populations [18] may have contributed to this process. Generally, it is desirable to implement a structured high-quality guideline process in each country to improve acceptance. An update of the EU consensus [22] would be helpful in establishing widely accepted state-of-the-art guidelines. The problem of HCV infection in IDUs is recognized in most EU countries. Guidelines represent 1 component in enabling access to treatment, accompaniment by implementation of outreach programs, qualification of professionals, and adequate funding.

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