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Regionalized Management of Medicine

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Translational Bioinformatics

Volume 17

Series Editor

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Translational bioinformatics is defined as the development of storage-related, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data, and genomic data in particular, into proactive, predictive, preventive, and participatory health. Translational bioinformatics includes research on the development of novel techniques for the integration of biological and clinical data and the evolution of clinical informatics methodology to encompass biological observations. The end product of translational bioinformatics is the newly found knowledge from these integrative efforts that can be disseminated to a variety of stakeholders including biomedical scientists, clinicians, and patients. Issues related to database management, administration, or policy will be coordinated through the clinical research informatics domain. Analytic, storage-related, and interpretive methods should be used to improve predictions, early diagnostics, severity monitoring, therapeutic effects, and the prognosis of human diseases.

Hui Shen • Yiming Zeng • Li Li •
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Regionalized Management of Medicine

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Preface

This book with a high focus on "Regionalized Management of Medicine" for this understanding originally stemmed from our improvement of understanding and vision in the importance and significance of "regionalization" during our medical practice, hospital management, and information sharing. The meaning of regionalization does not tell us to "limit" our knowledge and experience or make issues more confidential. In opposite, we highly encourage that data collection, storage, and preservation should be more open to reachable collaborators, partners, and societies. We highly encourage that the members of the regionalized alliance have the right to access legacy materials created with outdated technology. It is our passions to call the special attentions from researchers, clinicians, managers, and leaders on regionalized collaborations and development.

I also would like to express my deep appreciations to all co-editors, Hui Shen who is the president of Jinshan Hospital of Fudan University, Yiming Zeng who is the president of The Second Hospital of Fujian Medical University, and Li Li who is the director of Scientific Research and Education of Henan Province People's Hospital of Zhengzhou University, China, to all assistant editors, Feiyu Yang and Dongli, Song, and to all authors of chapters, for their efforts and supports as well as hard works. I also appreciate colleagues from Nature Springer for the great and unwavering efforts and supports.

"Regionalized Management of Medicine" is a new strategy to optimally perform medical practice and management. I expect more advances in regionalized management of medicine, especially in update of new biotechnology, application of therapeutic strategy, and understanding of disease-associated molecular mechanisms. I expect more developing in medical informatics, systems analysis, database sharing, and artificial intelligent for improving the quality of hospital managements, disease therapies, regional collaborations, and medical services in future.

Shanghai, China
October 20, 2021

Xiangdong Wang

Contents

About the Editors

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Xiangdong Wang, MD, PhD is a distinguished professor of medicine at Fudan University, director of Shanghai Institute of Clinical Bioinformatics, director of Fudan University Center of Clinical Bioinformatics, director of Shanghai Shanghai Engineering Research Center for AI Technology of Cardiopulmonary Diseases, deputy director of Shanghai Respiratory Research Institute, executive director of Clinical Science Institute of Fudan University Zhongshan Hospital, and visiting professor of King's College of London. He serves as the president of Chinese Society of Gene Technology and deputy president of National Committee of Clinical Precision Medicine, Chinese Medical Doctor Association. His main research is focused on single cell sequencing, clinical bioinformatics, disease-specific biomarkers, lung chronic diseases, cancer immunology, and molecular and cellular therapies. He is the author of more than 300 scientific publications with the impact factor about 1100, citation number about 9923, h-index 51, and i10-index 256.

Chapter 1
The Importance of Regionalized Management of Medicine

Hui Shen, Yiming Zeng, Qinqi Ling, Li Li, and Xiangdong Wang

Abstract The present book presents the new and international understanding, vision, and experience on regionalized management of medicine, including clinical practice, knowledge, methods, and effectiveness. The regionalized management is a new approach to gather all strengths, resources, and facilities and improve the effectiveness, efficiency, and outcome of medical services and clinical therapies.

Keywords Regionalized management · Clinical · Hospitals · Medicine

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Regionalized management of medicine is defined as the management of case, care, patient, disease, and therapy-associated activities that is regionalized according to geographical locations, culture-associated living, and collaboration-based regions. Regionalized management of medicine also includes the share of medical information, resource, transport/delivery, Internet medication, and new technologies. For example, fucoidan from brown seaweed was suggested to have various biological and pharmacological activities, especially anticancer/antitumor, anti-proliferation, and anti-inflammatory and immune-modulatory functions (Hsu and Hwang 2019). As a complementary therapy, fucoidan was applied to patients with cancer after operation or in severe condition in the scientific collaboration-based regions. Regionalized management of medicine plays an important role in clinical and translational medicine from bench to patient, from patient to bench, and from patient to policy, to improve the quality of life in patients as suggested (Cheng et al. 2020). Regionalized management of medicine is also a critical approach to face the unexpected challenge like COVID-19, since the current status of infection management lacks the regionalized management system and organization, dependent upon either the government or hospital itself. Clinical laboratory features to distinguish COVID-19 from community-acquired pneumonia were identified by a group/hospital (Pan et al. 2020), while those characters of routine laboratory tests failed to be shared among regional hospitals and be an efficient tool for clinical diagnosis and therapy.

Regionalized management of medicine is a shortcut to introduce and develop a new therapeutic strategy among hospitals. The "multidisciplinary therapy strategy of precision medicine" was proposed as a new approach for clinical practice, decision-making, and therapies for complicated cancer (Qian et al. 2020). The strategy provides optimal and precise therapy for the individual patient by integrating multidisciplinary experts and developing real-time therapeutic strategy based on clinical phenomes, gene sequencing of tissue DNA, and circulating DNA. In order to extend such strategy into regional hospitals, the Yangtze River Delta integration alliance of gene test was used as a platform to educate clinical nurses and physicians, train techniques and operations, and organize clinical practice of multidisciplinary therapy strategy of precision medicine. This can be an example of regionalized management in clinical application of gene sequencing for tumor therapy. Yan et al. shared the experience of regional alliance to measure gene sequencing to support clinical decision-making for target therapy and efficacy evaluation (Yan et al. 2021).

The aim of this book entitled *Regionalized Management of Medicine* is to share the understanding of regionalized management scope and definition, the experience of regionalized management of medicine in practice, and the knowledge of scientific and clinical research in molecular medicine. Hwang and Williams described the importance of medical informatics in management of patients with alcohol use disorder by using hospital system-wide solutions, managing patient populations, and supporting public health efforts (Hwang and Williams 2021). Regionalized management of medical information, informatics, clinical phenomes, and therapies can be an efficient approach to dynamically control and follow-up patients.

Precision medicine is an emerging approach for doctors to select individual treatments based on a genetic understanding of the disease. One of the most important issues in performance and regionalization of clinical precision medicine is to standardize management, technology, and standards of precision medicine. Tan et al. described the development and advancement in gene sequencing technologies, next-generation sequencing in clinic (Tan et al. 2021). Qian et al. emphasized the importance of precision medicine and headlined the understanding of "Clinical Precision Medicine" as an up-to-date resource on precision medicine and pathways toward clinical performance for clinicians and researchers (Qian et al. 2021). It is the first time to share their own typical workflow and experience of metagenomic gene sequencing in details, e.g., sample collection, nucleic acid extraction, library construction, sequencing, data analysis, and report writing. It is also the first time to introduce the standardization of clinical practice in metagenomic gene sequencing, interpretation of positive and negative results, and potential of regional application.

Artificial intelligence can be an important tool of regionalized management of medicine and is considered as the predictive and prognostic power of molecular biomarkers in clinical and translational medicine. For example, the DNp73 expression was identified as a predictive marker for the 5-year prediction and prognosis of the rectal cancer patients in aid of artificial intelligence management (Pham et al. 2020). Artificial intelligence was also found to be valuable to monitor the occurrence of acute lung injury in patients with COVID-19 infection and clinical phenomes of patients with COVID-19 infection (Li et al. 2020; Zhang et al. 2020). In this book, Briganti overviewed the importance of artificial intelligence as a tool to improve the quality of medical care, design of development studies, and models and testing the effectiveness (Briganti 2021). It is necessary to evaluate the strengths of regional medical resources and build bridges between the industrial and healthcare sectors. In addition to medical care, the artificial intelligent single cell was proposed as a single-cell-like system with computerized databases, digitalized informatics of biological elements, and programmed function and signals (Zeng et al. 2018). The artificial intelligent single cell can act not only as an optimal system with a full understanding of cell molecular profiles, intelligent capacity of functioning and deep learning, and precise interpretation of measurements but also as a decision-making assistant and a powerful tool to monitor clinical phenotypes and molecular networks in patient response to therapies, especially for regionalized management of medicine.

One of the most exciting issues here is that the book also combines new sights of understanding about deep science with frontline bioanalysis, to offer an example how to promote the advanced disciplines and talent development during hospital management. Huang et al. described the importance to translate the synthetic lethality to therapy by the synthesis of genetic interaction data from model organisms, tumor genomes, and human cell lines, and to identify nonintuitive targets for improving drug resistance (Huang et al. 2021). Tang et al. headlined the new understanding of epigenetics and DNA methylation in regulating gene expression throughout the genome, linking environmental factors with genetic susceptibility factors in lung diseases (Tang et al. 2021). With the rapid development of bioinformatics, clinical bioinformatics become more important and applicable for clinical

practice in the identification and development of disease diagnosis and prognosis prediction. Liu et al. addressed the important role of clinical bioinformatics in the understanding of pathogenesis, in the discovery of disease-specific biomarkers and therapeutic targets, and in the prediction of patient prognosis (Liu et al. 2021). This will benefit clinical mangers and leaders to understand the techniques of clinical bioinformatics and to solve clinical problems.

The experience of regionalized management from various locations is shared in the book. Ferna´ndez et al. demonstrated that the inventory management as an essential task was performed at the pharmacy department in Spain and presented different and contradictory optimization criteria, more challenges to be overcome, and advanced demand estimation methods and control techniques (Fernández et al. 2021). Dogan shared the experience and understanding of symptom and life quality management in patients with cancers in Turkey (Dogan 2021). Ling et al. shared a mode of the "Fudan-Minhang Medical Alliance" in China to develop a healthcare system for regionalized management on medical, educational, and research aspects of healthcare services (Ling et al. 2021). This is an approach to strengthen the regional medical management and improve the service quality and ability to reform the medical and health system. Belciuga discussed potential factors associated with bed-occupancy management and hospital planning in Romania, including diseases, patients' characteristics, cultural background, budget, local and national political considerations, and others (Belciuga 2021). This provides a management mechanism by which the efficacy of bed utilization can be improved. Jahan shared Japanese experience on management of severe childhood pneumonia in low resource setting, especially when clinic beds were limited in developing countries (Jahan 2021). This strategy on the basis of WHO guidelines can be realistic and applicable for developing and other developed and/or underdeveloped countries with cost-effectiveness. Pires et al. emphasized the importance and effectiveness of the mission in the management, which should be realistic, acceptable, implementable, and motivative (Pires et al. 2021).

In conclusion, the present book presents the new understanding, vision, and experience on regionalized management of medicine, including clinical practice, knowledge, methods, and effectiveness. The regionalized management is a new approach to gather all strengths, resources, and facilities and improve the effectiveness, efficiency, and outcome of medical services and clinical therapies.

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Chapter 2
Alcohol Use Disorders: Leveraging Informatics to Improve Patient Care

Calvin Hwang and Lyncan Williams

Abstract Alcohol use disorders (AUDs) is a worldwide public health problem. Incidence and severity may vary based on geography, culture, and individual genetics. Pharmacogenomics offers the potential for personalized medicine of patients with specific genetic profiles. Informatics may help clinicians better identify patients with have or are at-risk for AUD. It may also offer better, more standardized in-hospital and ambulatory treatments. Lastly, integrated informatics efforts may better inform decision makers of more effective public health approaches.

Keywords Alcohol use disorders · CIWA · SBI · Public health · EHR

2.1 Introduction

The use of electronic health records (EHRs) in clinical medicine has improved the detection, treatment, and prevention of alcohol use disorders in multiple settings. This chapter explores the various ways in which medical informatics has impacted laboratory research, clinical medicine, and finally, public health systems.

Worldwide, alcohol is the seventh leading risk factor for poor health. In 2016, it was estimated that alcohol was associated with three million deaths (5.3% of all deaths) and 132.6 million disability-adjusted life years (5.1% of all DALYs) (Fig. 2.1). Harmful alcohol use contributed to more than 200 diseases and injury-related health conditions, most notably DSM-IV alcohol dependence, liver cirrhosis, cancers, and injuries (WHO Alcohol Fact Sheet 2021).

According to the WHO, the European region continues to have the heaviest alcohol consumption in the world. It is estimated that of the 70% of Europeans

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Fig. 2.1 Total alcohol per capita consumption (APC) (15+ years; in liters of pure alcohol), 2016 Source: WHO. Global status report on alcohol and health 2018

who drink, 31.5% of men and 12.6% of women report heavy episodic drinking. On average, Europeans consume 10.7 L of pure alcohol each year. Average consumption of alcoholic beverages varies widely between WHO European Region member countries, from an average of 3.9% in the Southeast European subregion (Anon n.d.-a) to as high as 14.4% in the Eastern European subregion (Anon n.d.-b; WHO Regional Office for Europe, Alcohol Use 2021).

Use of alcohol in the USA mirrors that of Europe, with 55.3% reporting use in the past month and 26.5% reporting heavy episodic drinking (Substance Abuse and Mental Health Services Administration (SAMSA) 2021). In 2010, alcohol misuse cost the USA $249 billion with three-quarters of the total cost related to heavy episodic drinking (Sacks et al. 2015).

Though the prevalence of alcohol consumption in China is lower than most Western populations, it has increased more than 50-fold from 0.4 L in 1952 to 4.9 L in 2009 of pure alcohol (Cochrane et al. 2003). The China Kadoorie Biobank cohort found that 33% of Chinese men drink regularly (compared to 2% of women) with an increase in the proportion engaging in heavy episodic drinking increasing from 30 to 35% between 2004 and 2008 (Im et al. 2019). Left unchecked, this will have profound systemic health impacts in the future.

Much of the variation in alcohol use behavior may be due to cultural norms. Unlike many diseases, AUDs are often described in qualitative terms. For instance, in the ICD-10 diagnosis of alcohol dependence, one criterion includes "difficulties in controlling substance-taking behaviors in terms of its onset, termination, or levels of use." But loss of control may depend on normalization of culturally acceptable behavior (Marques et al. 2019). Without absolute benchmarks, it may be difficult to compare national perceptions of alcohol use (Rehm and Room 2017).

Some have recommended using Europeans as the standard or benchmark for alcohol consumption. Yet even in Europe, acceptable behavior may be contextual (e.g., permissible during festivals or weekends) or evolve over time (Rehm et al.

2005). Similar findings have been found worldwide in Switzerland (Haug and Schaub 2016), China (3), and Australian Aborigines (Haroon et al. 2018).

Furthermore, the quantity of alcohol consumed may not directly correlate with observed injuries or costs. Self-report population surveys may underdetect AUDs based on acceptable normalized behavior (Gmel et al. 2013; Probst and Rehm 2018). Populations which consider loss-of-control behavior unacceptable may have less tolerance for aggressive behavior, translating into lower rates of injury and death (Norström 2001).

The overwhelming fact is that excessive consumption of alcohol affects the economy of all countries or regions due to potentially preventable harm, lost revenues and productivity. Informatics may help in the early identification of at-risk individuals, provide cost-effective preventative strategies to mitigate use, provide targeted treatment for AUD, and support public health initiatives.

2.2 Use of Informatics in Laboratory Research

Alcohol use disorders (AUDs) arise from a combination of chronic response to alcohol exposure, individual genetic makeup, and environmental disturbances over time. In many people, alcohol use disorder behavior patterns are established during adolescence, which are modulated by genetically influenced individual risk profiles (Blomeyer et al. 2013). Known as candidate gene and environment interaction studies (cGxE), these studies have identified potential candidate genes that influence the development of alcohol addiction and maladaptive behavior. These candidate genes typically influence reward seeking, inhibition, systemic stress response, or alcohol metabolism (Kim and Park 2018).

Current research has shown that the genetic component of vulnerability to alcohol addiction is complex, does not follow clear Mendelian inheritance, and is not linked to a single gene. Widespread availability of genomic mapping and analysis now allows genome-wide association studies (GWASs) to identify candidate genes for multiple diseases, including alcoholism. GWASs of European populations identified alcohol dehydrogenase cluster variants associated with alcohol use disorders (Treutlein et al. 2009; Schumann et al. 2011; Stacey et al. 2012; Frank et al. 2012; Biernacka et al. 2013; Kapoor et al. 2013).

Advances in pharmacogenomics have also identified potential epigenetic mechanisms influencing the onset of addictive behavior. Genomic DNA methylation mapping (Zhang et al. 2014) and hypermethylation (Taqi et al. 2011) of alcohol-dependent patients support the theory that such changes arise as a consequence of, rather than a cause of, the disorder (Nieratschker et al. 2014). Reversal of such methylation may be examples for potential future pharmacologic treatment of alcohol use disorders.

Pharmacogenomics can be used to predict treatment response. Some studies have suggested that functional single nucleotide polymorphism (SNP) in the μ-opioid receptor gene may predict clinical response to naltrexone (Oslin et al. 2003; Anton

et al. 2008; Kranzler et al. 2013; Chamorro et al. 2012). Similarly, genetic variations in GAT-binding protein 4 may influence treatment response to acamprosate (Kiefer et al. 2011; Mann et al. 2013). Other potential treatment candidates identified using genomic analysis of SNPs include topiramate and ondansetron, as well as sensitivity to benzodiazepines (Zastrozhin et al. 2019). Pharmacogenomics offers the potential for personalized treatment of AUDs.

2.3 Use of Informatics in Clinical Medicine

During the past decade, informatics has begun to positively impact the treatment and prevention of AUDs in several clinical settings: emergency departments, hospitalized inpatients, ambulatory practice, and adolescent medicine.

2.3.1 Emergency Medicine

In 2018, US motor vehicle drivers with blood alcohol concentrations (BAC) above 0.08 accounted for nearly one-third of all traffic-related deaths, or 10,511 (Thomas et al. 2019). This resulted in an estimated economic cost in 2010 (the most recent year that cost data is available) of $44 billion including direct and indirect costs. The impact of elevated BAC on driving has been well described. Effects include impaired coordination, judgment, self-control, loss of balance, concentration, and situational awareness (Anon 2020).

Among 25 European Union members, the number of traffic fatalities officially attributed to alcohol declined by nearly 50% between 2006 and 2016 from 4950 to 2630 (Fig. 2.2) (European Transport Safety Council 12th Annual Road Safety Performance Index (PIN) Report 2020). But there is widespread consensus that the real number of alcohol-related deaths may be as high as twice the reported rate due to several factors. These include inconsistent national definitions of deaths attributed to drunk driving, lack of systematic testing of all drivers involved in collisions, and use of police records as the sole data source (World Health Organization (WHO) 2012). Thus, international comparisons of the impact of drunk driving may not be possible.

Studies have not conclusively found direct associations between elevated BAC and clinical outcomes such as injury severity scores, in-hospital mortality, or discharge disposition in survivors (Ahmed and Greenberg 2019; Demetriades et al. 2004; Stübig et al. 2012; Lowenfels and Miller 1984; Maier 2001). Thus, the benefit of alcohol screening in trauma patients may be more impactful with the potential reduction of future harm rather than at the time of the incident.

In the USA, alcohol screening in emergency departments is performed by hospitals voluntarily participating in the National Trauma Data Bank. Similar collaboratives exist elsewhere, such as in Germany (German In-Depth Accident Study) and Canada (British Columbia Trauma Registry).

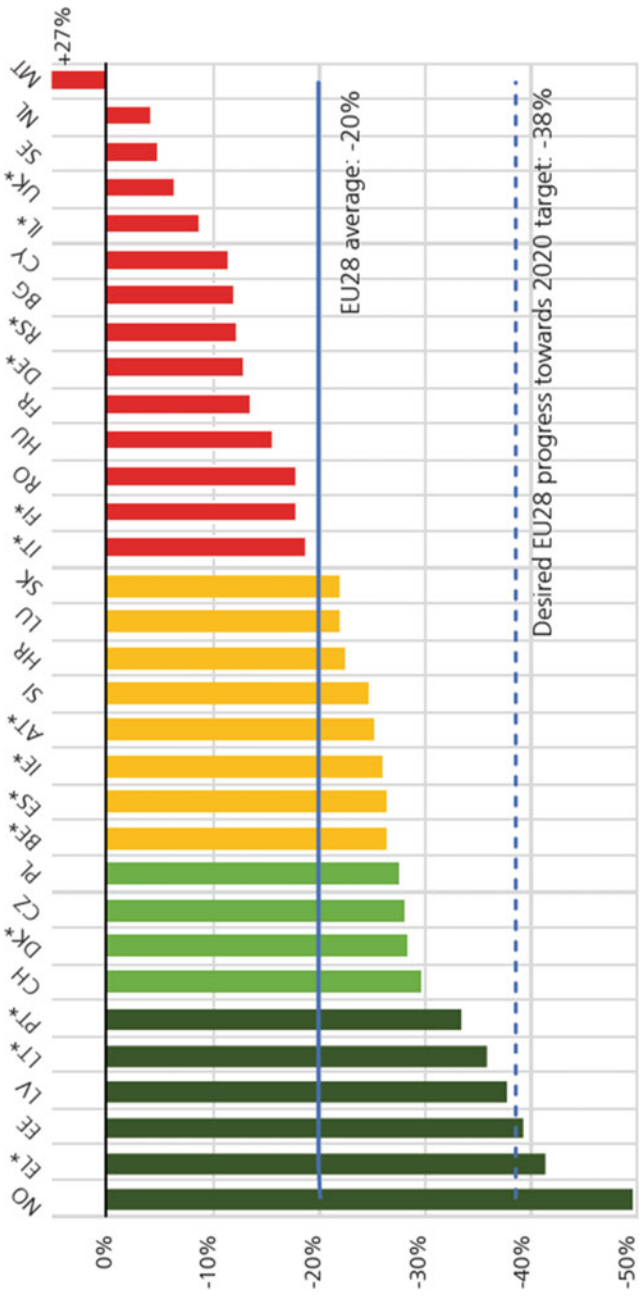

Fig. 2.2 Relative change (%) in European traffic fatalities between 2010 and 2017
Source: European Transport Safety Council 12th Annual Road Safety Performance Index (PIN) Report, accessed Aug 4, 2020

The American College of Surgeons Committee on Trauma (ACS/COT) began focusing on alcohol screening and brief intervention in 2006. Participating level 1 and level 2 trauma hospitals were required to develop protocols for alcohol screening and brief intervention (SBI). This mandate, however, did not specify which patients to screen, leading many centers to screen a limited subset of patients (Schermer 2005; Cunningham et al. 2010; Schermer et al. 2003; Terrell et al. 2008).

Some studies found that having an elevated BAC was the best blood test for detecting hazardous alcohol use (Savola et al. 2004). Not surprisingly, 71% of trauma centers used BAC as their sole method for alcohol screening (Schermer 2005). However, as much as 40% of trauma patients with hazardous alcohol behavior may be undetected based on BAC alone (Ewing et al. 2012).

A few studies of ED-based SBI programs have found positive results. One meta-analysis demonstrated that ED-based SBIs were correlated with fewer alcohol-related injuries at 6 or 12 months without an impact on ED visits or admissions (Landy et al. 2016).

A Scottish government medical informatics project linking anonymized personal healthcare records with core datasets found slightly different results. These datasets included medical outpatient attendance, inpatient admission, psychiatric inpatient admissions, emergency department visits, and pharmacy dispensing records. Targeted SBI of emergency department patients was associated with a reduction of emergency department visits for 2 years, while outpatient and inpatient usage returned to baseline by the end of the study period (Baldacchino et al. 2018).

Despite encouraging evidence of the effectiveness of ED-based SBIs, significant barriers exist. Factors include EHR system heterogeneity, lack of IT support and resources, funding, and resistance among clinical staff (Van Eaton et al. 2014). Studies examining the potential financial benefits of a coordinated SBI on a community-wide or national scale have yet to be published.

2.3.2 Adult Inpatient Medicine

The use of medical informatics in the inpatient hospital setting has focused primarily on treatments of alcohol withdrawal syndrome (AWS). Shaw first described the use of an objective alcohol withdrawal symptom scale, known as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A), in 38 chronic alcoholics admitted for AWS (Shaw et al. 1981). Foy et al. used the CIWA-A scale to guide treatment for AWS and found that higher scores were correlated with higher risk of severe withdrawal (Foy et al. 1988). Sullivan et al. later demonstrated that a pure symptom-based CIWA scale (CIWA-Ar) without the use of traditional clinical vital signs – such as tachycardia or elevated blood pressure – resulted in similar reliability as the original scale (Sullivan et al. 1989). The CIWA scale and its variants have been validated in several countries outside of the USA including Australia (51), Germany (Stuppaeck et al. 1994), and India (Sachdeva et al. 2014) (Fig. 2.3).

PHARMACOLOGICAL TREATMENT AND REASSESSMENT PARAMETERS

CIWA-Ar Score	Orders		
≤7	No treatment necessary. Reassess CIWA score every four (4) hours. If score remains ≤7 for 24 hours, contact provider to discontinue the protocol.		
8-10	Chlordiazepoxide 50mg PO every one (1) hour PRN. Reassess CIWA score every hour and re-dose as needed to achieve CIWA < 8.		
11-12	Diazepam 5 mg IV every ten (10) minutes PRN for CIWA score of 11-12. Reassess CIWA score every ten (10) minutes and re-dose as needed to achieve CIWA <11.	OR	LORazepam 1 mg IV every twenty (20) minutes PRN for CIWA score of 11-12. Reassess CIWA score every 20 minutes and re-dose as needed to achieve CIWA <11.
13-15	Diazepam 10 mg IV every ten (10) minutes PRN for CIWA score of 13-15. Reassess CIWA score every ten (10) minutes and re-dose as needed to achieve CIWA <13.	OR	LORazepam 2 mg IV every twenty (20) minutes PRN for CIWA score of 13-15. Reassess CIWA score every twenty (20) minutes and re-dose as needed to achieve CIWA <13.
≥16	Diazepam 10 mg IV every ten (10) minutes PRN for **Obtain ICU consult. Reassess CIWA score every ten (10) minutes and re-dose as needed to achieve CIWA <16.	OR	LORazepam 2 mg IV every twenty (20) minutes **Obtain ICU consult. Reassess CIWA score every twenty (20) minutes and re-dose as needed to achieve CIWA <16.

Fig. 2.3 Example of CIWA-Ar protocol used for EHR implementation
Source: Melkonian et al. (2019)

Since then, CIWA-Ar-based protocols have been incorporated into the EHRs of many individual hospitals. Most use benzodiazepines as the main treatment medication. Results have demonstrated significant clinical and operational improvements. Use of a symptom-triggered approach to AWS treatment has resulted in significant reductions in average medication dosage (Foy et al. 1988; Saitz et al. 1994; Reoux and Miller 2000; Eberly et al. 2016; Melkonian et al. 2019), duration of treatment in inpatient detox units (Shaw et al. 1981; Foy et al. 1988), inpatient length of stay (LOS) (Foy et al. 1988; Saitz et al. 1994), delirium tremens (Jaeger et al. 2001), and incidence of mechanical ventilation (Saitz et al. 1994; Sen et al. 2017). One study found no difference in outcomes including harm but was limited by a high exclusion rate and significant variation in protocol adherence (Waye et al. 2015).

Pope demonstrated that by linking nutritional supplements to the CIWA-Ar order set, more patients received appropriate doses of multivitamins, thiamine, and folate (Pope et al. 2016).

Other medications have been used as well with CIWA-Ar-based protocols. These include barbiturates (Askgaard et al. 2016; Tidwell et al. 2018), baclofen (Girish et al. 2016), and dexmedetomidine (Woods et al. 2015) but with mixed results.

Some critics of CIWA-Ar-based protocols argue that these protocols are often implemented after symptom onset, thus missing an opportunity for AWS prophylaxis. The Alcohol Use Disorders Identification Test (AUDIT) has been studied as a predictive tool for the development of AWS (Bohn et al. 1995; Dolman and Hawkes 2005). Another tool is the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) (Maldonado et al. 2015). Further research is required to determine if use of a predictive AWS tool prior to implementation of an AWS treatment protocol (such as CIWA-Ar) improves clinical outcomes.